The Body as a Depth

Illness and recovery read as closure, without an actor

J. Konstapel
Constable Research, Leiden · November 2026

Abstract

Medicine describes the body as an agent. It defends, repairs, adapts and fails. This essay sets out a different way of looking. It starts from one rule about what persists. It applies that rule depth by depth, from chemistry to tissue, organ, rhythm and mind. A body is then not an actor. It is a depth: a set of configurations that close and therefore remain.

In this view illness is a configuration that stays open, or one that closes on the wrong form. Recovery is a change in which closed configuration lies nearest. No part of the body needs to know the right form. The essay states the rule, derives the main laws, and restates illness and cure without agent verbs. It also reports a full recomputation. Most laws hold exactly. Three earlier results needed correction. One new result, a repair rule without a template, follows from the geometry of the rule itself. The essay ends with the tests that can fail and with the questions that remain open.

1. Why another way of looking

Open any textbook of physiology. The verbs are those of a person. The immune system recognises. The cell decides. The brain predicts. The body heals itself. These verbs are useful. They are also a hidden theory. They assume a subject that knows how things should be and acts to restore it.

Biology has argued about this for a long time. Mayr called it teleonomy: behaviour that looks purposeful but follows a programme. The word saved the appearance of purpose. It did not remove the actor. It moved the actor into the programme.

This essay goes one step further. It drops the actor altogether. There are only configurations. Some close and remain. Others do not close and pass. What we call health and what we call illness are both configurations that remain. They differ only in how they relate to a reference form.

This is not a matter of style. Verbs steer research questions. "Why does the body fail to repair?" asks for a missing capacity. "Which closed configuration lies nearest, and how far away is it?" asks for a distance. The second question can be counted. Much of this essay is that count.

2. The ground: one strand, one rule

2.1 Crossings carry direction, not quantity

The starting picture is a single strand that crosses itself. At a crossing the strand passes one way, passes the other way, or does not cross. A crossing has no size. It has a direction. In this text the three states are written +, − and 0. The signs are shorthand for direction. They are not amounts.

Three consecutive crossings form a **window**. A window **closes** when its three directions cancel modulo three. There are 27 possible windows. Exactly 9 close.

Kind	Number	Example	Character
Uniform: three the same	3	(+,+,+)	Holds. Does not turn.
Mixed: three different	6	(−,0,+)	Turns at every step and stays closed.
Open	18	(+,+,0)	Does not close. Does not remain.

One selection rule follows. What closes remains. What does not close passes on as tension to its neighbours. There is no selector outside the rule.

2.2 Two ways to close

The two kinds of closure matter for everything that follows. A uniform window holds but cannot turn. It is the form of a crystal. A mixed window keeps turning while it stays closed. Every crossing changes, yet the closure holds. It is the form of living matter.

Mixed windows come in two families. One runs (−, 0, +) and its rotations. The other runs (+, 0, −) and its rotations. They are mirror images. They are the two living directions.

2.3 The same rule as geometry

The 27 windows can be laid out as a cube of three by three by three cells. Each axis carries one crossing. Read in the Clifford algebra of three-dimensional space, each cell becomes an oriented element of space. The nine closed cells then have a clear shape.

- The centre (0,0,0) is the scalar: a point without orientation.
- The two poles (+,+,+) and (−,−,−) are the oriented volume and its mirror.
- The six mixed cells form a hexagon in the plane where the three directions cancel. They carry the three planes of rotation, each twice.

The hexagon is the quaternion frame: pure rotation. So the living, mixed closures are rotations. The uniform closures are the point and the volume. This reading adds one fact that the next sections need. A mixed window and its mirror carry the same plane of rotation with opposite sign. In quaternion terms they are q and −q. They describe the same rotation, one turn of 2π apart in a cover of 4π.

> *Status. The counts are exact and were recomputed by full enumeration. The geometric reading follows the published mapping of the trit cube onto Cl(3).*

2.4 Rings and the period-three law

A ring is a strand closed on itself. Ask that every window of a ring be closed. Then the directions must repeat with period three. The proof is two lines. Two neighbouring windows share two places. If both close, the places they do not share must be equal.

Two consequences follow at once. Uniform rings exist at every length. Mixed rings exist only when the length is a multiple of three. There are then exactly two of them, one for each living direction. A living ring therefore grows only by whole groups of three.

3. The body is a depth

The same rule repeats upward. What closes at one depth becomes the alphabet of the next. This is widening and pruning. Units combine. Only what closes persists. A body is not a separate object to which the rule is applied. A body is simply one depth of the same strand.

At each depth the rule yields exact counts. Some match known biology without further assumptions.

Depth	Exact law	What it matches
Word	Readable words of three letters over four symbols, without uniform words and one phase per rotation: $(4^3 - 4)/3 = 20$.	Twenty amino acids. Same count as the comma-free code of Crick, Griffith and Orgel.
Copy	Every direction has one partner: x meets only −x.	Semi-conservative replication; antiparallel pairing.
Membrane	Nine closed leaflets of length nine; in eight of nine the partner leaflet differs.	Measured asymmetry of plasma-membrane leaflets.

Depth	Exact law	What it matches
Cell division	A closed ring of six cut anywhere gives two closed rings of three in the parent direction.	Division into two closed daughters.
Tissue	A chain closes only if it repeats one word in one phase.	Tissue as units kept in register.
Organ	Two different words never close together. k kinds leave at least k − 1 open seams.	Organs held by carriers: blood, nerve, hormone.
Circulation	A lasting carrier loop meets k seams for k organ kinds and runs one way.	Closed circulation with valves.

Two kinds of thing exist at every depth. Closed forms hold: atoms, cells, organs. Unclosed forms pass: light between atoms, a hormone between cells, a word between people. Only what passes can deliver. A closed form returns its tension to itself and hands nothing over. That carriers decay is what keeps a body readable. Each message is gone once it has been read.

4. A language without an actor

If there is no actor, cause and effect lose their usual meaning. In a one-strand picture there are not two separate things to draw an arrow between. Four terms take the place of cause.

- **Selection by fit.** Only what returns in step remains.
- **Identity over depth.** The same winding, read at another depth.
- **Constitutive relation.** A state that holds at once. There is no arrow and no sequence.
- **Correspondence.** A measured pattern that has the form of a rule.

The common phrases of medicine can be rewritten in these terms. The rewrite is not cosmetic. Each line removes an assumption.

Usual phrase	Restated	Assumption removed
The body repairs itself.	Of the closed configurations, the nearest one remains.	A repairer that knows the target.
The immune system recognises a threat.	A meeting of two forms has one of three outcomes: fit, misfit or unread.	A judge.
The tumour escapes detection.	What was not read as misfit is what remains. The tumour is the remainder of a selection.	An evader with a strategy.
The cure works against the body.	After a partial change the old closed form is still nearest.	Two parties in conflict.
Therapy gives the patient a new form.	An added strand changes the places of the joint configuration, and so what lies nearest.	A reader who carries the right form.

> *Status. These are restatements, not new claims. Where a statement in this essay still uses a verb such as "repair", it is shorthand for the right-hand column.*

5. Illness as a configuration

Open windows arise all the time. Health is not their absence. An open window is not yet an illness. Illness is an open window that persists, or a closure on the wrong form. Eight configurations cover every case. Each rests on one exact law.

Code	Configuration	Exact law	Reading in a body
S	Seam	A uniform stretch never closes against a mixed stretch.	Something fixed lodged in something living: plaque, stone, scar, deposit.
D	Direction	Two mixed stretches of opposite direction never close end to end.	Rhythms that run against each other or against the day.
U	Unread	An error opens three windows and stays while no meeting reads it.	Cancer, latent infection, a deposit nothing clears.
O	Over-read	A meeting gives misfit where the form fits.	Autoimmunity, allergy.
C	Carrier	No organ closes as one strand. Its seams stay open unless something passes across them.	Ischaemia, stroke, hormone loss, conduction block.
W	Wrong closure	Past one third of a form wrong, the nearest closed form is no longer the original.	Stable wrong states: depression, chronic pain, addiction.
F	Frame and copy	A word is read in one phase. A copy is exact only through its partner.	Frameshift, repeat expansion, mutation.
R	Drift	Openings arrive faster than closure can follow within one period.	Ageing, frailty, slow loss of rhythm.

The configurations combine. A heart attack is S followed by C. Type 1 diabetes is O followed by C. Dementia is U, S and R together.

Form W deserves attention. A wrong closure is closed. Every window in it is closed. A meeting with it gives "fit". It therefore persists for exactly the same reason that a healthy form persists. Health and wrong closure are not function and malfunction. They are two closed states. Only a reference form tells them apart. This is why a wrong closure does not resolve on its own. Nothing in it is open.

The frame law gives a clean clinical test. A deletion of a whole number of words keeps the reading frame. Any other deletion shifts it. In the dystrophin gene this predicts two diseases from one gene. Measured: frame-keeping deletions give the milder Becker form and frame-shifting deletions give the severe Duchenne form, in about nine of ten cases.

> *Status. The laws are exact. Their naming in a body is a reading. The Becker–Duchenne match is a reproduction of measured data.*

6. The meeting without a judge

When two forms meet, there are three outcomes and only three. They fit. They do not fit, and the misfit is taken apart. Or the meeting does not register, and nothing happens. The third outcome is the important one. A form that is never read is neither kept nor removed. It simply remains.

Two failures mirror each other. A misfit can register as "nothing" or as "fit". It remains. That is form U. A fit can register as "misfit". It is taken apart. That is form O. A change that makes meetings register more strongly reduces the first failure and increases the second. A change that weakens them does the reverse.

Measured medicine shows both sides. Checkpoint inhibitors strengthen the registration of misfits. They cure some cancers. Their main harm is inflammation of healthy organs. Immunosuppressants weaken it. They treat autoimmune disease. Their main harm is infection and, over years, some cancers. The law gives one rule. Read the direction of the failure first. Then move only the other way.

Cancer reads simply in this language. Copying makes lasting changes every day. Meetings take apart what registers as misfit. What accumulates over years is therefore only what did not register. A tumour is the remainder of that selection. Nothing in it chose to hide. The autopsy record agrees: many people who die of other causes carry small tumours that never grew.

7. Direction and phase

Two different departures from a living ring must be kept apart. A **reversal** turns the direction: (−,0,+) becomes (+,0,−). A **phase slip** keeps the direction but shifts the start: (−,0,+) becomes (0,+,−). The recomputation in this essay shows that they cost different amounts at a seam.

Join of two different closed words	Fewest open windows at the seam
Uniform against mixed	1
Mixed against mixed, opposite direction (reversal)	1
Uniform against a different uniform	2
Mixed against mixed, same direction, other phase (phase slip)	2

A reversal is cheaper at the seam than a phase slip. The cube explains why. A phase slip moves the rotation to another plane. A reversal keeps the plane and flips the sign: q becomes −q. It is the same rotation, one turn further round the double cover.

Over a whole form the picture is different. A living form of 27 places differs from its reversal in 18 places. It differs from the uniform forms in 18 places too. It differs from its own phase-shifted copies in all 27. So the nearest other closed states of a living form are its reversal and its flattening. They are not a shifted copy of itself.

This gives a sharp reading of disorders of mood. A reversal is near: cheap to join, two thirds of a form away. A flattening is equally near. A form pushed too far closes onto one of these two. In this reading mania and depression are the two nearest wrong closures of one living form. The uniform closure is the flat, fixed state of severe depression. The reversal is the state that runs the other way.

The same seam law applies to circulation. Each change of direction in a loop of living units costs at least one open window. A loop that carries without new openings must run one way. Measured anatomy has closed loops and valves.

> *Correction. An earlier computation gave two open windows per reversal. It held the phase of each segment fixed. With the phase free, the minimum is one. The one-way conclusion is unchanged.*

8. Recovery as a change of what is nearest

8.1 One error, one place

Change one place of a closed ring. Exactly three windows open: those that contain the place. For a ring of four or more places, these three windows share only that one place. So exactly one single change closes them again. It is the return of that place to its earlier direction. Any change elsewhere leaves at least one window open.

This is often read as "repair must happen at the right place". That reading hides a template. Who knows the right place and the right value? The geometry answers without one. The right place is the

only place that lies inside all three open windows. The right value is the only value that closes them. Both are given by the open windows themselves.

This was tested. A living ring of 81 places received one random change per round for 200 rounds. After each change one rule was applied: take the place that lies in the most open windows, and give it the direction that closes most of them. No copy of the original was used.

Rule applied after each change	Open windows after 200 rounds (of 81)	Places differing from the original
Nothing	54	53
A random place gets a random direction	54	54
A random place in an open window gets its best direction	40	54
The place in most open windows gets its best direction	0	0

The last rule keeps the ring fully closed and fully original. It needs no template and no knower. The overlap of the open windows is enough.

> *Correction. An earlier version reported 64 open windows without repair. The expected value is two thirds of 81, which is 54. The earlier report of zero open windows for "repair at the error site" was true by construction, because it undid a known error. The overlap rule above replaces it with a result that is not.*

8.2 The limit of density

The overlap rule has a limit. It works when openings arrive one at a time. When two openings fall close together before closure follows, their windows overlap. The rule then finds a closed form, but not always the original one.

Changes and closures per round	Open windows after 200 rounds	Places differing from the original
1 and 1	0	0
2 and 2	10	26
3 and 3	15	45

This adds a second bound to recovery. The first bound is the share of a form that is wrong. The second is how many openings arrive within one period of closure. A form can be well below one third wrong and still drift, if its openings come in clusters.

8.3 The limit of one third

Now let many places be wrong at once. Let the outcome be the nearest closed configuration. A living ring of 27 places gives this:

Wrong places (of 27)	Back to original	Reversal	Uniform	Shifted copy	Exact tie
up to 8	100 %	0	0	0	0
9	99.99 %	0	0	0	0.01 %
12	93.6 %	1.0 %	1.0 %	0	4.3 %
15	29.6 %	20.3 %	19.9 %	0.6 %	29.7 %

Wrong places (of 27)	Back to original	Reversal	Uniform	Shifted copy	Exact tie
18	0 %	31.8 %	31.9 %	12.6 %	23.8 %

Up to eight wrong places the outcome is always the original. At exactly a third a tie becomes possible, with probability 0.012 %. Beyond a third the reversal and the flattening take over. These are closed, so nothing in them is open. This is form W.

8.4 The dose of a change

A change that turns a living form into its reversal must alter 18 of 27 places. Suppose k of those changes have been made when the next closure period comes. The form is then k places from the old closure and 18 − k from the new one. The nearest one remains.

Changes made (of 18)	All aimed: new form	Three quarters aimed: new form	Three quarters aimed: old form	Other closed form
0 to 8	0	0	1	0
9	½	0.038	0.962	0
10	1	0.385	0.615	0
11	1	0.799	0.196	0.004
12	1	0.959	0.013	0.028
17 to 18	1	0.988	0	0.012

The law is sharp. Fewer than half of the changes, and the old form returns in full. More than half, and the new form remains. When a quarter of the changes miss, two thirds are needed for a 96 % outcome. A change spread thinly over many periods is undone in each one. It helps only while it is renewed.

> *Note. These values are exact sums, not samples. They assume that an exact tie between two closed forms is shared equally. At ten changes with a quarter missing, 28 % of outcomes are such ties. The tie rule is therefore part of the law and is stated here explicitly.*

8.5 What an added strand can and cannot do

A wrong closure has no open window. So nothing inside it points the way back. Something must be added. But adding a closed strand changes nothing on its own. A closed day rhythm joined to an opened body leaves the same three windows open. The sum of closed and open is open.

What helps is an addition that changes places in the joint configuration. A fixed wake time, a therapist in an exposure session, a stimulator in the brain: each changes which closed configuration lies nearest. None of them needs to carry or know the right form. The dose law then says how much must change within one period.

Measured treatment shows this shape in several places. One night of sleep deprivation lifts about half of depressed patients. The gain is usually gone after the next sleep. Holding the new placement with phase advance and morning light keeps it. One long session for a specific phobia works about as well as many weekly ones. A large, fast weight loss brings remission of type 2 diabetes in nearly half of patients. Slow, small losses rarely do. Each match is a reading. The law predicts something not yet tested: the same total change works when concentrated within one period, and fails when spread out.

9. Rhythm, sleep and the day

Time in this view is a coordinate, not a substance. A rhythm is a winding that returns. Persistent rhythms repeat with period three. The day is the one rhythm the body does not make. It must be joined.

That join has a cost. Cut a living rhythm at the end of a whole cycle and join it to a day of the same direction: no window opens. Cut it within a cycle, or join it to a day of the opposite direction: at least one window opens. Waking is free only at a cycle end and only in the direction of the day.

Two measured patterns agree. The night tends to end just after a sleep cycle closes. The 24-hour regularity of activity is lower in depression. The second law predicts more. In a body out of step with the day, waking should not cluster at cycle ends. Each waking leaves something open. That is a candidate for the unrefreshing early waking of depression. It is a test that can fail.

A second bound limits how far apart a rhythm and its closure period may lie. A form of 9 places tolerates a period ratio of about 0.2. A form of 81 places tolerates about 0.9. Larger forms can wait longer than in proportion to their size. Sleep reads as the period in which openings are fewest and closure can catch up. The law says that such a period is needed. It does not give its length. That needs the rate of openings, which the rule does not give.

10. Cure ordered by depth

If illness is a configuration at a depth, cure is a change at that depth. Interventions then sort into five layers.

Layer	What changes	Fits forms	Examples
Mesh	Remove, rebuild or replace a part.	S, C, U	Surgery, thrombectomy, transplant.
Chain	Restore one molecular step.	C, F, U	Insulin, thyroxine, targeted drugs, gene therapy.
Meeting	Shift how meetings register, in one direction.	U, O	Vaccines, checkpoint inhibitors, biologics.
Phase	Restore rhythm and direction.	D, W, R	Sleep timing, light, exercise, rehabilitation, psychotherapy.
Surround	Change what everyone is exposed to.	All	Clean air, tobacco control, water, salt policy.

Three consequences follow. A layer helps only the forms it fits. Keyhole surgery on a worn knee did no better than sham surgery. A chain-layer drug for a phase failure helps only while it is taken. Weight returns when semaglutide stops.

Second, a change in the meeting layer works one way only. Read the direction before acting.

Third, the phase layer is the least used. Yet it is the only layer that fits D, W and R. Those are the forms of ageing, of most mental disorders and of the chronic diseases of rhythm. That is where this view places the frontier of medicine.

Prevention sits below the ladder. One error has one place of return. A form past one third closes wrongly and cannot return by itself. Prevention keeps forms below that limit and keeps openings apart in time. The largest measured effects at the lowest cost come there: vaccination, stopping smoking, folic acid before conception, daily sunscreen, time outdoors for children.

11. What was tested, and what failed

A view like this must name where it fails. Tests were fixed before the data. They are reported with their misses.

11.1 Protein chains

Each residue of a protein was written by its charge at neutral pH: lysine and arginine as +, aspartate and glutamate as −, all others as 0. The test used all 20,429 reviewed human proteins in UniProt, 11.4 million residues. Each protein was compared with shuffled copies of itself.

Measure	Real	Shuffled	Ratio
Closed windows	53.75 %	52.52 %	1.023
Uniform closed windows	47.68 %	46.28 %	1.030
Mixed closed windows	6.07 %	6.25 %	0.972

Real chains close more often than chance, by about 69 standard deviations. But the excess is uniform. Mixed, living closure is slightly depleted. A closer look explains why. Three quarters of residues are uncharged. Of all uniform windows, 98.6 % are (0,0,0). Ninety per cent of the closure excess comes from runs of uncharged residues. Those are membrane segments and hydrophobic cores. Among windows with at least one charge, a smaller excess remains. It comes from runs of equal charge. Same-charge pairs are enriched at short spacing more than opposite-charge pairs at any spacing.

So this writing rule measures how charge clusters in blocks. It does not measure living closure. The prediction as fixed passes. The more interesting claim fails. The failure points at the writing rule, not at the closure rule.

11.2 Helices

Opposite charges meet most often three and four residues apart. That is the geometry of the α-helix, with 3.6 residues per turn. It is not a multiple of three. Over whole turns the α-helix repeats after 18 residues in 5 turns, which is a multiple of three. Five of eight common helix types share this property ($p = 0.088$, suggestive only). Coiled coils pack with a seven-residue repeat, 3.5 per turn: close to three but not three. Local geometry wins at this depth. The rule of three shows only when whole turns are counted.

11.3 Rhythms

Predictions about closure itself tend to hit. Body rhythms lock at rest. Locking is strongest in deep sleep and absent in REM and waking. The night tends to end after a cycle closes. Predictions that isolate the number three tend to miss. The pattern is consistent across depths. Closure is real. The integer three dominates only where nothing else constrains the form.

12. What this changes in practice

The view does not replace clinical medicine. No cure here was found by it. It offers three other things.

- **One map.** Many different interventions fit on it. It says why so many routes help the same disease: they act at different depths on one configuration.
- **Different questions.** Not "what does the body fail to do?" but "which closed state is nearest, and how far is it?" Distance can be estimated. Dynamical systems research already measures it indirectly. Slowing recovery from small disturbances precedes both the onset and the end of depressive episodes. That is a measurable sign that another closed state is close.

- **Tests that can fail.** A concentrated change should work where the same change spread out fails. Waking in depression should not cluster at cycle ends. A slow taper should hold where an abrupt stop does not. Each can be tested with existing data or simple trials.

13. Open questions

- **Why the nearest?** Every recovery law here assumes that the nearest closed configuration remains. The assumption is natural. It is not yet derived from the selection rule itself.
- **Ties.** The dose law needs a rule for exact ties. Equal sharing is the simplest. Another rule would change the numbers near the threshold.
- **Rates.** The density bound needs the rate at which openings arrive. The rule does not supply it.
- **Writing rules.** Each depth needs a choice of what counts as a crossing. Charge was a poor choice for proteins. Other choices must be fixed before data and tested.
- **Magnitude.** A crossing carries direction, not size. How sizes enter, through a second register of tension, is still to be derived.

14. Conclusion

A body is a depth. It is made of configurations that close and therefore remain. Illness is a configuration that stays open, or one that closes on the wrong form. A wrong closure persists for the same reason health does. Recovery is a change in which closed configuration lies nearest. The right place for that change is given by the overlap of open windows. No part of the body needs to know the right form.

Most of this follows from one rule and can be counted. The counts were redone. They hold, with three corrections and one new result. Where the view meets measured data, closure itself tends to hold and the bare number three tends to fail. That pattern is itself informative. It says where the rule is enough and where each depth adds its own geometry. What remains open is stated. The rest can be tested.

Annotated references

The references are ordered by theme. Each note says why the source matters for the argument and where to go next.

Foundations and geometry

Konstapel, J. (2026). De kubus waarin de volledige natuurkunde past: from quaternions to Vacuum.Net, mapping four theories onto Cl(3). constable.blog, 2 October 2026. https://constable.blog/2026/10/02/russell-larson-clerk-maxwell-and-the-vacuum-net-theory-on-the-clifford-algebra-of-apace/

Maps the 27 cells of the trit cube onto the blades of Cl(3). The source for section 2.3: centre, poles and hexagon, and the double cover that explains why a reversal is cheaper than a phase slip. Start here for the geometric side.

Hestenes, D. & Sobczyk, G. (1984). *Clifford Algebra to Geometric Calculus.* Dordrecht: Reidel.

The standard text on geometric algebra. Explains blades, bivectors as planes of rotation and the even subalgebra as quaternions. Read chapter 1 for the background of section 2.3.

Rowlands, P. (2007). *Zero to Infinity: The Foundations of Physics.* Singapore: World Scientific.

Builds physics from a nilpotent algebra in which the total sums to zero. The closest established relative of the closure rule used here. Useful for readers who want the physics below chemistry.

Purpose, landscape and attractors

Mayr, E. (1961). Cause and effect in biology. *Science* 134, 1501–1506.

Separates proximate from ultimate causes and introduces teleonomy into wide use. Shows how biology kept the appearance of purpose. Section 1 argues for going one step further.

Waddington, C. H. (1957). *The Strategy of the Genes.* London: Allen & Unwin.

The epigenetic landscape: development as a ball rolling into valleys. The nearest classical image for "the nearest closed configuration remains". The difference here is that the valleys are counted, not drawn.

Kauffman, S. A. (1969). Metabolic stability and epigenesis in randomly constructed genetic nets. *Journal of Theoretical Biology* 22, 437–467.

Cell types as attractors of a network. A precedent for reading stable biological states as closed configurations rather than goals.

Huang, S., Ernberg, I. & Kauffman, S. (2009). Cancer attractors: a systems view of tumors from a gene network dynamics and developmental perspective. *Seminars in Cell & Developmental Biology* 20, 869–876.

Reads cancer as a stable but abnormal state of the network. Close to form W and to the reading of the tumour as a remainder. Compare with section 6.

Transitions and early warning

Scheffer, M. et al. (2009). Early-warning signals for critical transitions. *Nature* 461, 53–59.

Shows that systems near a tipping point recover more slowly from small disturbances. Offers a measurable proxy for the distance to another closed state. Basis of the practical proposal in section 12.

van de Leemput, I. A. et al. (2014). Critical slowing down as early warning for the onset and termination of depression. *PNAS* 111, 87–92.

Finds early-warning signals in mood data before depressive episodes begin and end. The most direct empirical link to the reading of depression as a wrong closure.

Codes, copying and frames

Crick, F. H. C., Griffith, J. S. & Orgel, L. E. (1957). Codes without commas. *PNAS* 43, 416–421.

Derives 20 as the size of the largest comma-free code of triplets over four letters. The count in section 3 reproduces this number by another route.

Golomb, S. W., Gordon, B. & Welch, L. R. (1958). Comma-free codes. *Canadian Journal of Mathematics* 10, 202–209.

Proves the general maximum $(k^3 - k)/3$ for comma-free codes of length three. The formula used in section 3.

Meselson, M. & Stahl, F. W. (1958). The replication of DNA in *Escherichia coli*. *PNAS* 44, 671–682.

The experiment that showed semi-conservative copying. Reproduced by the unique-partner law.

Monaco, A. P. et al. (1988). An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics* 2, 90–95.

Frame-keeping deletions give Becker, frame-shifting deletions give Duchenne dystrophy. The clinical test of the frame law in section 5.

Aartsma-Rus, A. et al. (2006). Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle & Nerve* 34, 135–144.

Confirms the frame rule in about nine of ten of more than four thousand patients. Read it for the exceptions, which mark where the rule needs more than the frame.

Lorent, J. H. et al. (2020). Plasma membranes are asymmetric in lipid unsaturation, packing and protein shape. *Nature Chemical Biology* 16, 644–652.

Measured asymmetry of the two leaflets of mammalian plasma membranes. Set beside the derived asymmetry of closed leaflets.

Protein geometry

The UniProt Consortium (2025). UniProt: the Universal Protein Knowledgebase in 2025. *Nucleic Acids Research* 53, D609–D617.

The source of the 20,429 reviewed human proteins used in section 11.1, downloaded 12 November 2026. Anyone can repeat the test from this data.

Pauling, L., Corey, R. B. & Branson, H. R. (1951). The structure of proteins: two hydrogen-bonded helical configurations of the polypeptide chain. *PNAS* 37, 205–211.

Origin of the α-helix with 3.6 residues per turn. Explains why opposite charges meet three and four apart.

Marqusee, S. & Baldwin, R. L. (1987). Helix stabilization by Glu^{-}…Lys^{+} salt bridges in short peptides of de novo design. *PNAS* 84, 8898–8902.

Shows that salt bridges at spacing i, i+4 stabilise helices more than at i, i+3. Matches the charge-pair profile of section 11.2.

Crick, F. H. C. (1953). The packing of α-helices: simple coiled-coils. *Acta Crystallographica* 6, 689–697.

The first account of the coiled coil and its seven-residue repeat. The 3.5-per-turn compromise is the nearest the helix comes to a period of three.

Lupas, A. N. & Gruber, M. (2005). The structure of α-helical coiled coils. *Advances in Protein Chemistry* 70, 37–78.

A thorough review of coiled-coil geometry and sequence rules. The place to start for a test of closure on helix-resolved structures.

Immune selection

Dunn, G. P., Old, L. J. & Schreiber, R. D. (2004). The three Es of cancer immunoediting. *Annual Review of Immunology* 22, 329–360.

Elimination, equilibrium and escape. The phases are correct. Section 6 differs only in its verbs: what the data show is a remainder, not an escape.

Treatment evidence

Cipriani, A. et al. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs. *The Lancet* 391, 1357–1366.

All 21 drugs beat placebo with modest effects. Shows the chain layer helping while given, and the need to combine layers.

Golden, R. N. et al. (2005). The efficacy of light therapy in the treatment of mood disorders. *American Journal of Psychiatry* 162, 656–662.

Meta-analysis of light therapy, with effect sizes of 0.53 for non-seasonal and 0.84 for seasonal depression. Evidence for the phase layer.

Noetel, M. et al. (2024). Effect of exercise for depression: systematic review and network meta-analysis. *BMJ* 384, e075847.

Walking, jogging, yoga and strength training all reduce depression. A phase-layer intervention with effects comparable to drugs.

Richards, D. A. et al. (2016). Cost and outcome of behavioural activation versus cognitive behavioural therapy for depression (COBRA). *The Lancet* 388, 871–880.

Behavioural activation is as effective as CBT and cheaper. A change in placement through the day, not an added substance.

Lean, M. E. J. et al. (2018). Primary care-led weight management for remission of type 2 diabetes (DiRECT). *The Lancet* 391, 541–551.

Large, fast weight loss gave remission in nearly half of patients. The clearest measured case of the dose law: concentrated change crosses the threshold.