

What Fits, Stays

Designer Molecules, the Closure Rule of the Vacuum.Net, and Three Simple Roads to a Medicine

J. Konstapel, Leiden, 10 October 2026.

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1. The occasion

On 7 October 2026 the organic chemist Hermen Overkleeft of Leiden University received the Spinoza Prize of €1.5 million. Two days later *Het Parool* described his work.

The report contains six facts.

1. His group builds designer molecules. Each resembles a natural sugar molecule, with a small change.
2. A marker molecule sticks to one enzyme. The enzyme can then be followed live in the cell. The cell is not disturbed.
3. In some hereditary metabolic diseases one enzyme is too slow. The group built a molecule that slows the two enzymes before it. The whole line slows down. The complaints decrease.
4. Other molecules switch a harmful enzyme off completely.
5. One molecule, built for another protein, also stuck to an enzyme that cancer researchers had sought for decades. The body holds about 20,000 kinds of protein.
6. The collection holds about 7,000 compounds, dried, in jars. Anyone who writes receives a sample for the cost of postage.

The drug for the metabolic diseases is in a late test phase. It may be in use by the end of 2027. The report adds one sentence about the road: turning academic work into a medicine is slow and very expensive.

This essay reads the six facts with one rule of the Vacuum.Net theory. It then asks what the rule says about making medicines in a simpler way.

2. The rule

Picture a fishnet stretched in water. Strands cross in knots. Each knot carries one of three values: +1, 0 or -1. One such value is a trit.

Three neighbouring knots form a window. A window is closed when its three values add to a multiple of three. An open window carries tension.

There are $3 \times 3 \times 3 = 27$ windows. Nine are closed.

- Three are uniform: the same value three times. This is the form of a crystal. It does not change.
- Six are mixed: +1, 0 and -1 in some order. This form can keep turning while it stays closed. It is the form of living matter.

Two consequences are used below.

Two fix the third. With two values of a window given, exactly one value closes it.

A fixed knot closes one step in three. A turning window passes through three values. A knot held at one value matches one of them. Where a fixed form touches a turning form, a window stays open.

3. Where the work sits on the ladder

The net has a measuring rod of 45.6 nm. Each layer is a factor of three. Layer n has the size $3^n \times 45.6$ nm. The position of a thing is the number of factors of three between it and the rod.

Three sizes matter here.

- A sugar ring is about 0.5 nm. $0.5 / 45.6 = 0.01096$. The logarithm to base three is -4.11 . That is layer -4 , which measures $45.6 / 81 = 0.563$ nm.
- An enzyme is about 5 nm. $5 / 45.6 = 0.1096$. The logarithm is -2.01 . That is layer -2 , which measures $45.6 / 9 = 5.07$ nm.
- A cell is about 10 μm . $10,000 / 45.6 = 219.3$. The logarithm is 4.91. That is layer 5, which measures $243 \times 45.6 \text{ nm} = 11.08 \mu\text{m}$.

The closure rule sorts the layers into three families. Every third layer carries the same state. Family A holds layers 1, 4, 7 and -2 , -5 . Family B holds 2, 5, 8 and -1 , -4 . Family C holds 0, 3, 6 and -3 , -6 .

What	Size	Position	Layer	Family
Sugar ring, designer molecule	0.5 nm	-4.11	-4	B
Strand of DNA	2 nm	-2.85	-3	C
Enzyme	5 nm	-2.01	-2	A
Cell	10 μm	4.91	5	B

Two things follow.

The sugar, the strand of DNA and the enzyme sit on three neighbouring layers. Together they form one window, with one member of each family. The material, the pattern and the worker of the cell are a closed set of three.

The designer molecule and the cell belong to the same family. In a closed chain they carry the same state. The molecule is nine layers smaller than the cell, and it is in step with it. The enzyme between them is not.

4. The four finds, read with the rule

4.1 The marker: a reading

The body tests itself continuously. Each test has three outcomes. It fits and stays. It does not fit and is cleared. Or it is not read, and then nothing happens.

The third outcome is where illness hides. A slow enzyme is not cleared, because nothing reads its tempo.

The marker changes that. It sticks to one enzyme at layer -2 and leaves the cell at layer 5 as it was. It turns "not read" into "read". It is an instrument of diagnosis before it is anything else.

4.2 The brake: a treatment of tempo

Take the line of enzymes as a row of windows. The supply offers one window per step. A healthy enzyme closes one window per step.

Let the faltering enzyme close one window per k steps. Then $1 - 1/k$ of a window stays open at every step. With $k = 3$, two thirds stay open. After 300 steps, 200 open windows have piled up. That pile is the tension the patient feels as illness.

Now slow the supply to one window per k steps. Supply and closure are equal. The pile grows by $1/k - 1/k = 0$.

Nothing was repaired. The enzyme is as slow as before. Only the measure of the line was restored. That is the whole therapy.

The report says two enzymes before the faltering one are slowed. The rule gives that number a place. Two fix the third. The two set enzymes and the faltering one form one window. Set two, and the third closes.

4.3 The full stop: a fixed knot

Some molecules switch an enzyme off for good. In the rule this is a fixed knot. It closes one step in three, and its neighbours stop turning.

That is the wrong tool where a living form must keep turning. It is the right tool where the turning form is itself the deviation, as in some blood cancers. The rule separates the two cases. The brake restores measure. The full stop removes a winding.

4.4 The unplanned find: fitting selects

The molecule was built for one protein. It also stuck to another, among 20,000. Nobody designed that. It fitted, so it stayed.

The first axiom of use in the net is the same sentence. A winding persists only where it returns in phase inside its mesh. What does not fit does not stay. The cell performed the search that decades of design had not.

5. Three simple roads to a medicine

5.1 Fitting before design

The common road starts with a target. It then designs a key for that one lock, and tests one pair at a time.

Count the pairs. 7,000 compounds against 20,000 proteins is 140 million pairs.

The net reverses the order. Offer one key to living tissue. The tissue holds all 20,000 locks at once. The marker reads where the key stayed. One experiment covers 20,000 pairs. The whole collection takes 7,000 experiments, not 140 million.

The means exist. The keys are in jars in Leiden. They travel by post. Remaking one from the publications takes about a year. The reading instrument is the marker of Section 4.1.

What is missing is a map: which key closes on which layer, in which tissue. That map is a table, built from readings. It is small work compared with a design programme.

5.2 Measure before substance

The brake works through tempo. Tempo can be set in more than one place.

Where the supply comes from food, the meal is the brake. Phenylketonuria has been treated this way since 1953. The enzyme stays slow for life. The supply is lowered at the table. The child grows up healthy.

Where the body makes the supply itself, a molecule is needed at layer -2 . The diseases in the report are of that kind.

The order follows from the layers. Tension that arises between a body and its day closes only there. So the first questions are about the day: light and dark, sleep, the time of the meal, whole food. The substance comes after, where the layers above cannot reach.

5.3 State before substance

The fourth axiom of the net says that constants are functions of the local state. A mesh sets that state. A rate then follows.

Three measured points exist.

- Beryllium-7 inside a cage of sixty carbon atoms decays faster. The half-life drops from 53.12 to 52.68 days. That is 0.83%.
- A chemical reaction between two mirrors, tuned to a vibration of the molecule, ran up to 5.5 times slower. No light was supplied.
- The enzyme pepsin, in water between two mirrors tuned to the vibration of water, worked about 4.5 times slower.

Set the third point beside Section 4.2. A brake for $k = 3$ must slow the supply by a factor of three. The reported factor for an enzyme between mirrors is 4.5. The size is in range.

On this road the medicine is not a molecule. It is a mesh: a structure that sets the tempo of a window without adding a knot to it. Nothing is swallowed. Nothing has to be cleared afterwards.

This road is not built. The measurements were made in a laboratory cell, not in tissue, and later attempts to repeat some of them gave mixed results. One number is open: how far a mesh shifts the tempo of an enzyme inside a living cell.

6. The people

The diseases in the report are rare and hereditary. They show mostly in young children, in the cells of the brain. A child loses, month by month, what it had learned. A family lives for years with a name for the disease and nothing to do.

For these families the first road matters most. It shortens the finding. The second road matters for the far larger group whose line has lost its measure through the day they live in, not through an inherited enzyme.

The jars matter too. A researcher in a poor country receives the same sample as one in a rich country. A key that is shared can be tried in more tissues than a key that is owned. Fitting needs many tries. Sharing is what makes them possible.

The testing in people remains. It is the slow and costly part of the road. The three roads shorten the search before it. They do not replace the care with which a child is given something new.

7. Status of this essay

- **From the report.** The six facts of Section 1, the prize, the expected date.
- **From the theory.** The closure rule, the nine closed windows, the fixed knot at one in three, the ladder and its families, the fourth axiom.
- **Computed here.** The positions -4.11 , -2.01 and 4.91 . The pile of open windows and its removal. The 140 million pairs against 7,000 experiments.
- **Read.** Sugar, DNA and enzyme as one window. The two slowed enzymes as "two fix the third". The marker as a reading. The unplanned find as selection by fitting.
- **Measured elsewhere.** The cage, the slowed reaction, the slowed enzyme.
- **Open.** The map of keys per layer. The shift a mesh gives to an enzyme in a living cell.

Annotated references

The occasion

Van Agteren, P. (2026). "Door in Leiden te 'prutsen' met moleculen komt een medicijn voor ernstige ziektes een stuk dichterbij." *Het Parool*, 9 October 2026. *Why read?* The six facts of this essay in one page, in the researcher's own images: the assembly hall, the bottle factory, the jars. *Reading advice:* the passage on the brake and the passage on the unplanned find.

The net

Konstapel, J. (2026). *Two Kinds of Closure: The Katwijk Pill Factory Read Through One Rule of the Net.* Constable Research, Leiden, 1 October 2026. *Why read?* The closure rule, the 27 windows, the crystal form and the living form, and the fixed knot that closes one step in three. *Reading advice:* parts 2 and 3 for the derivation.

Konstapel, J. (2026). *Where Illness Comes From: The Net from First Chemistry to the Human.* Constable Research, Leiden. *Why read?* The test with three outcomes, and illness as what is not read. Section 4.1 rests on it. *Reading advice:* chapters 5 and 6.

Konstapel, J. (2026). *The Climate on the Ladder of Three.* Constable Research, Leiden, 3 October 2026. *Why read?* The measuring rod of 45.6 nm, the layers and the three families. Every position in Section 3 can be recomputed from it. *Reading advice:* Section 3 and Appendix A.

Konstapel, J. (2026). *Elements on Demand*. Constable Research, Leiden, 9 October 2026. *Why read?* The statement that a mesh sets a state and a rate follows, with the measured record kept apart by standing. *Reading advice:* Sections 6.2 and 8.

The designer molecules

Witte, M. D., Kallemeijn, W. W., Aten, J., et al. (2010). "Ultrasensitive in situ visualization of active glucocerebrosidase molecules." *Nature Chemical Biology* **6**, 907–913. *Why read?* A marker of the kind described in Section 4.1: it sticks to one sugar-cutting enzyme and shows it in the living cell. *Reading advice:* the images first, then the text.

Cravatt, B. F., Wright, A. T., and Kozarich, J. W. (2008). "Activity-based protein profiling: from enzyme chemistry to proteomic chemistry." *Annual Review of Biochemistry* **77**, 383–414. *Why read?* The general method behind the first road: one probe offered to a whole cell, read for where it stays. *Reading advice:* the sections on competitive profiling.

Wu, L., Jiang, J., Jin, Y., et al. (2017). "Activity-based probes for functional interrogation of retaining β -glucuronidases." *Nature Chemical Biology* **13**, 867–873. *Why read?* A published case from the Leiden laboratory in which probes for one class of enzymes also labelled heparanase, an enzyme tied to the spread of tumours. The newspaper does not name its enzyme; this paper shows the kind of find it describes.

The brake

Platt, F. M., Neises, G. R., Dwek, R. A., and Butters, T. D. (1994). "N-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis." *Journal of Biological Chemistry* **269**, 8362–8365. *Why read?* The first statement of the idea of Section 4.2: do not repair the slow enzyme, slow the supply. Four pages.

Cox, T., Lachmann, R., Hollak, C., et al. (2000). "Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin to decrease substrate biosynthesis." *The Lancet* **355**, 1481–1485. *Why read?* The brake in patients. It shows what restoring the measure of a line does for a person, and how long it takes.

Bickel, H., Gerrard, J., and Hickmans, E. M. (1953). "Influence of phenylalanine intake on phenylketonuria." *The Lancet* **262**, 812–813. *Why read?* Two pages. One child, one diet, and the proof that the meal can be the brake. The founding case of the second road.

The mesh

Ohtsuki, T., Yuki, H., Muto, M., Kasagi, J., and Ohno, K. (2004). "Enhanced electron-capture decay rate of ^7Be encapsulated in C_{60} cages." *Physical Review Letters* **93**, 112501. *Why read?* A cage changes a rate by 0.83%. Small, clean and undisputed.

Ebbesen, T. W., et al. (2012). "Modifying chemical landscapes by coupling to vacuum fields." *Angewandte Chemie International Edition* **51**, 1592. *Why read?* The founding paper of the field that changes chemistry with a cavity and no light. Its title states the premise.

Thomas, A., George, J., Shalabney, A., et al. (2016). "Ground-state chemical reactivity under vibrational coupling to the vacuum electromagnetic field." *Angewandte Chemie International Edition* **55**, 11462–11466. *Why read?* The reaction that ran up to 5.5 times slower between two

mirrors. *Reading advice:* the figure of rate against mirror distance; the effect appears only at the tuned distance.

Vergauwe, R. M. A., Thomas, A., Nagarajan, K., et al. (2019). "Modification of enzyme activity by vibrational strong coupling of water." *Angewandte Chemie International Edition* **58**, 15324–15328. *Why read?* The only measured point for an enzyme: pepsin, about 4.5 times slower. It is the number against which the third road must be judged.

Imperatore, M. V., Asbury, J. B., and Giebink, N. C. (2021). "Reproducibility of cavity-enhanced chemical reaction rates in the vibrational strong coupling regime." *Journal of Chemical Physics* **154**, 191103. *Why read?* An attempt to repeat an earlier cavity result that did not find the effect. It shows why the open number of Section 5.3 must be measured again, in tissue, before anything is built on it.