RNA self-assembly: Cooperation at the origins of life

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the timeline of life

Joyce (2002) *Nature* **418**, 214–221.

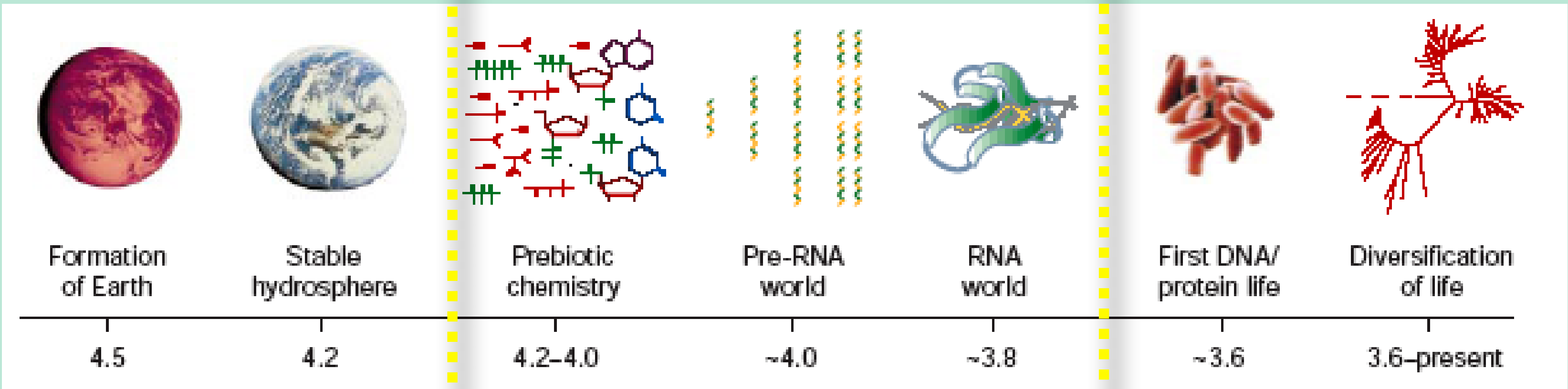


Figure 1 Timeline of events pertaining to the early history of life on Earth, with approximate dates in billions of years before the present.

LIFE = "a self-sustaining chemical system capable of darwinian evolution" (Joyce/NASA)

the origin of life ≈ the origin of self-replication?!?

the origin of <u>self</u>-replication...

but what is “self”?

RNA molecule

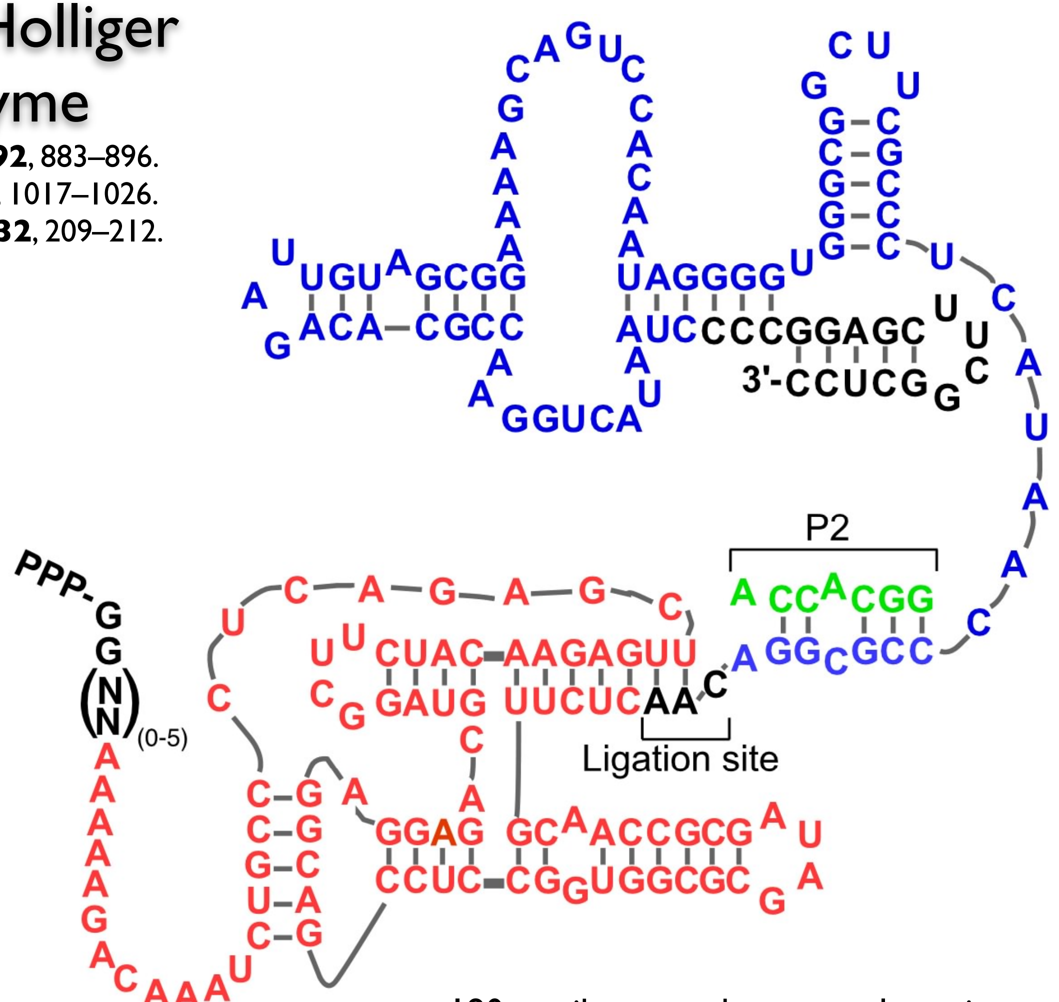
bacterium

SH-NW

molecular self-replication: **selfish** or cooperative?

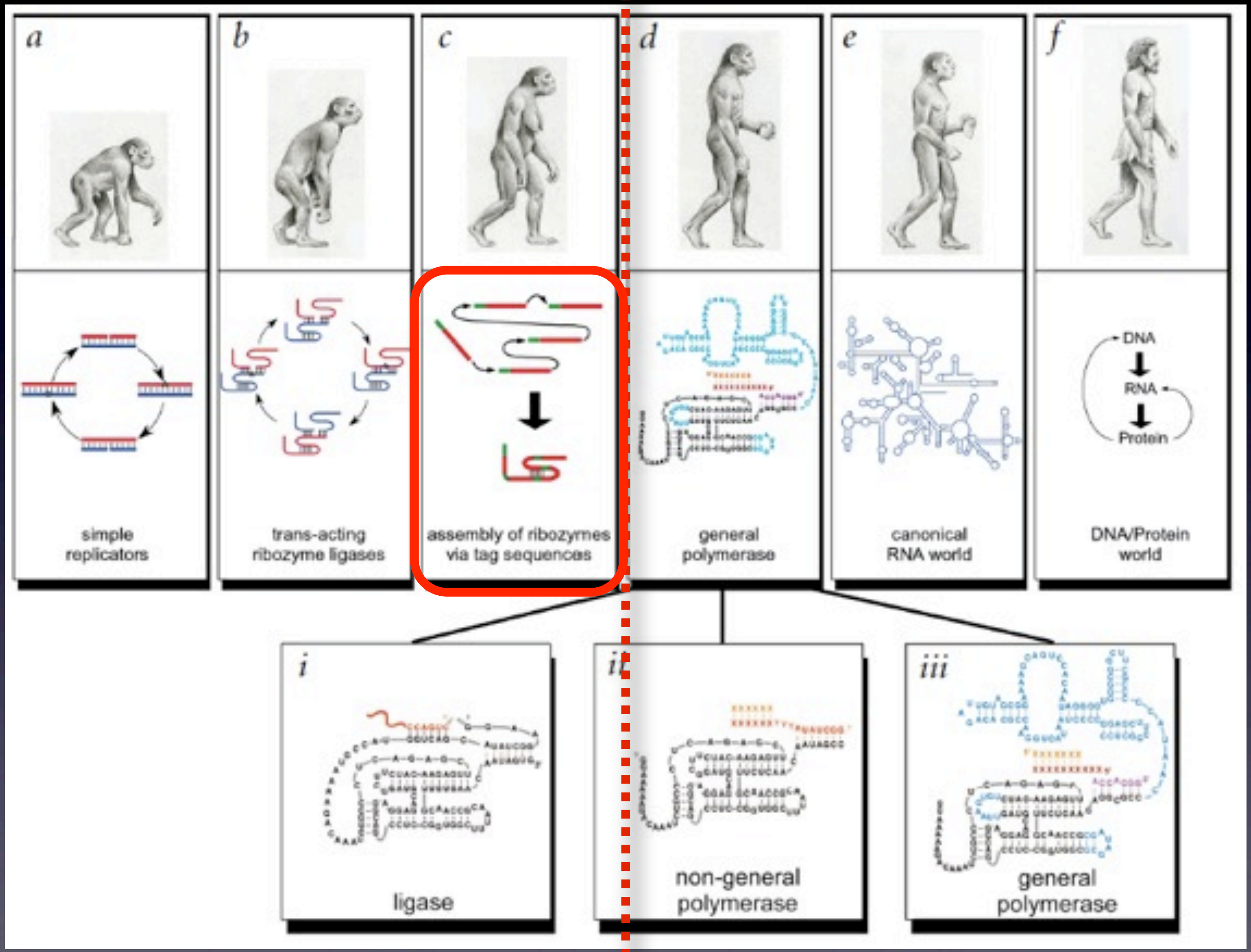
the Bartel/Unrau/Holliger replicase ribozyme

Johnston *et al.* (2001) *Science* **292**, 883–896.
Zaher & Unrau (2007) *RNA* **13**, 1017–1026.
Wochner *et al.* (2011) *Science* **332**, 209–212.



a 190-nt ribozyme that can polymerize a portion of itself

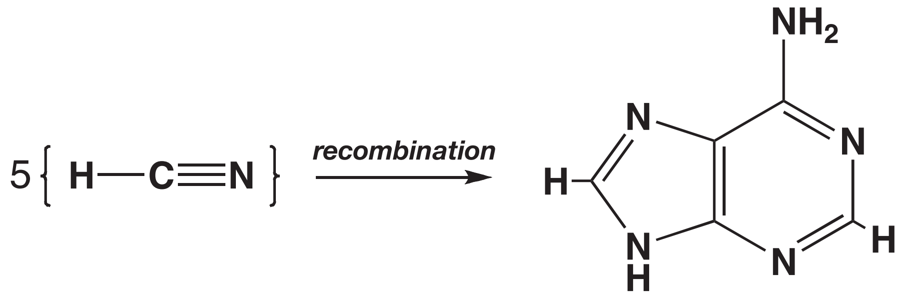
perhaps: cooperate ... then be selfish?



Levy and Ellington (2001) "The descent of polymerization"
Nat. Struct. Biol. **8**, 580–582.

“chemical cooperation”

hydrogen cyanide (HCN)



adenine

15 atoms &
50 electrons:
5 C-H bonds
5 C-N bonds

present in
interstellar medium

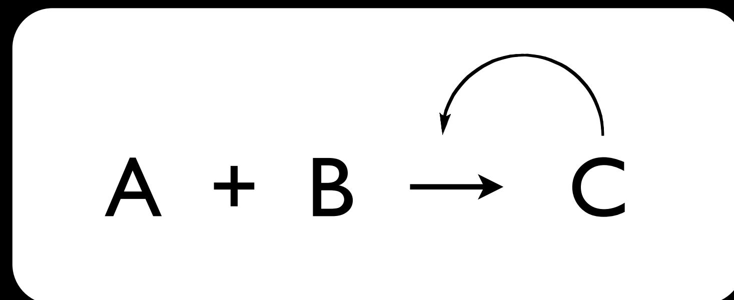
15 atoms &
50 electrons:
2 C-H bonds
9 C-N bonds
3 N-H bonds
1 C-C bond

present in
living systems

the Oró HCN polymerization experiments (1961)

autocatalysis

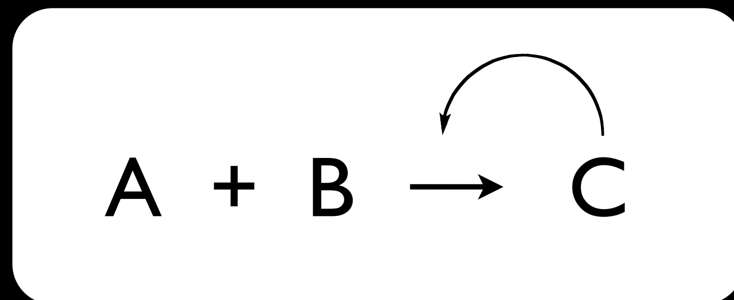
the chemical requirement for self-replication



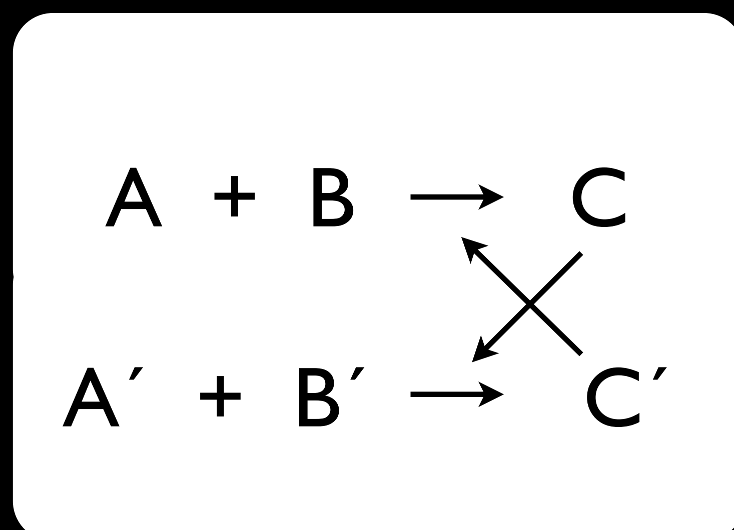
the product of a reaction catalyzes its own formation

but when did the "self" become strict?

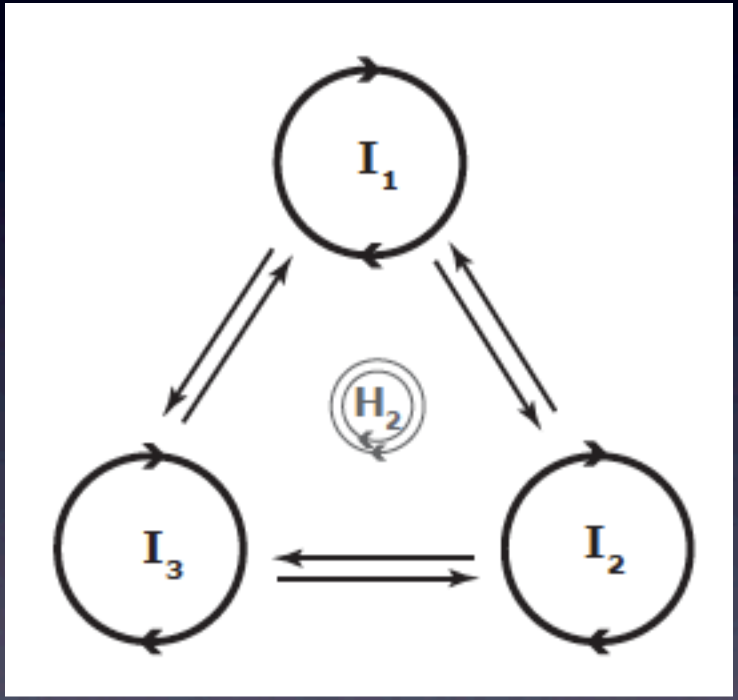
"selfish"



"cooperative"



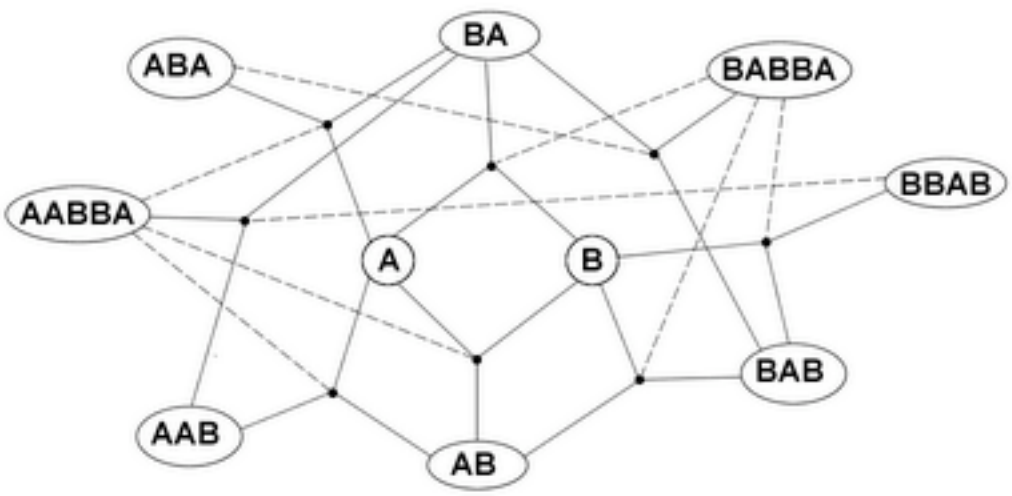
extending cooperation to >2 "selves"...



Eigen & Schuster, 1977; 1978

perhaps even a **cooperative network**?

an autocatalytic set



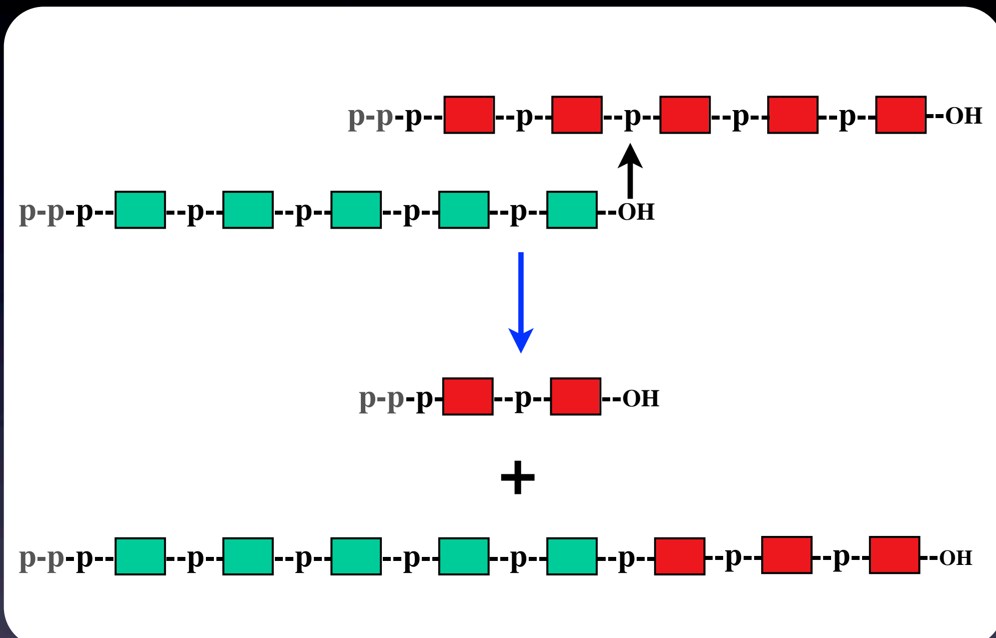
Kauffman (1993)

Q: can we create a cooperative network in the laboratory with catalytic RNAs?

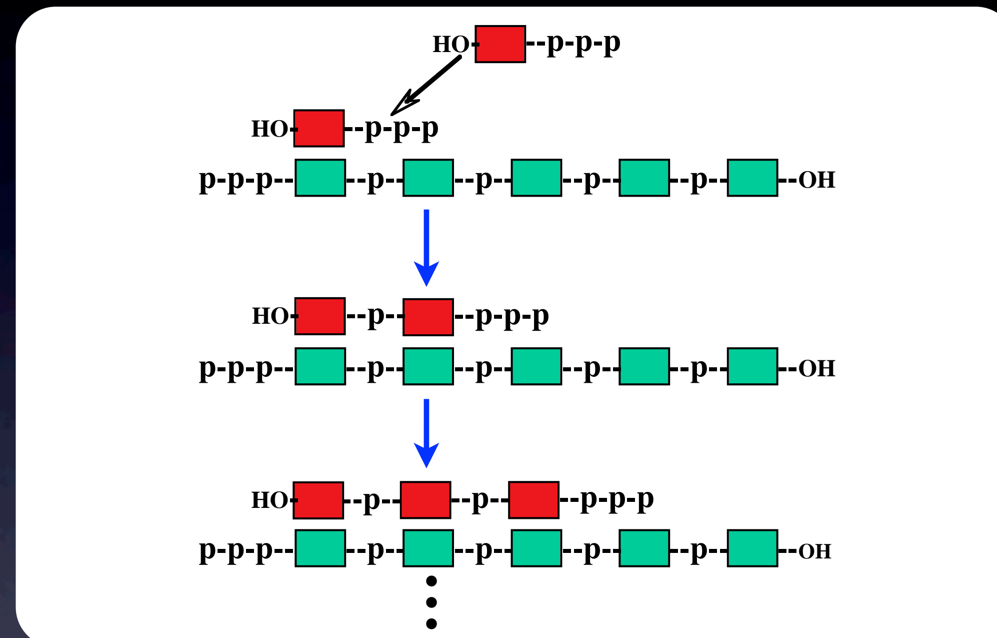
A: yes, by using catalytic RNA molecules that use recombination to piece together more copies of themselves

recombination!

Recombination, at the molecular level, is the breaking and re-ligation of (phosphoester) bonds resulting in the swapping of ≥ 1 monomer units between two nucleic-acid strands



recombination



polymerization

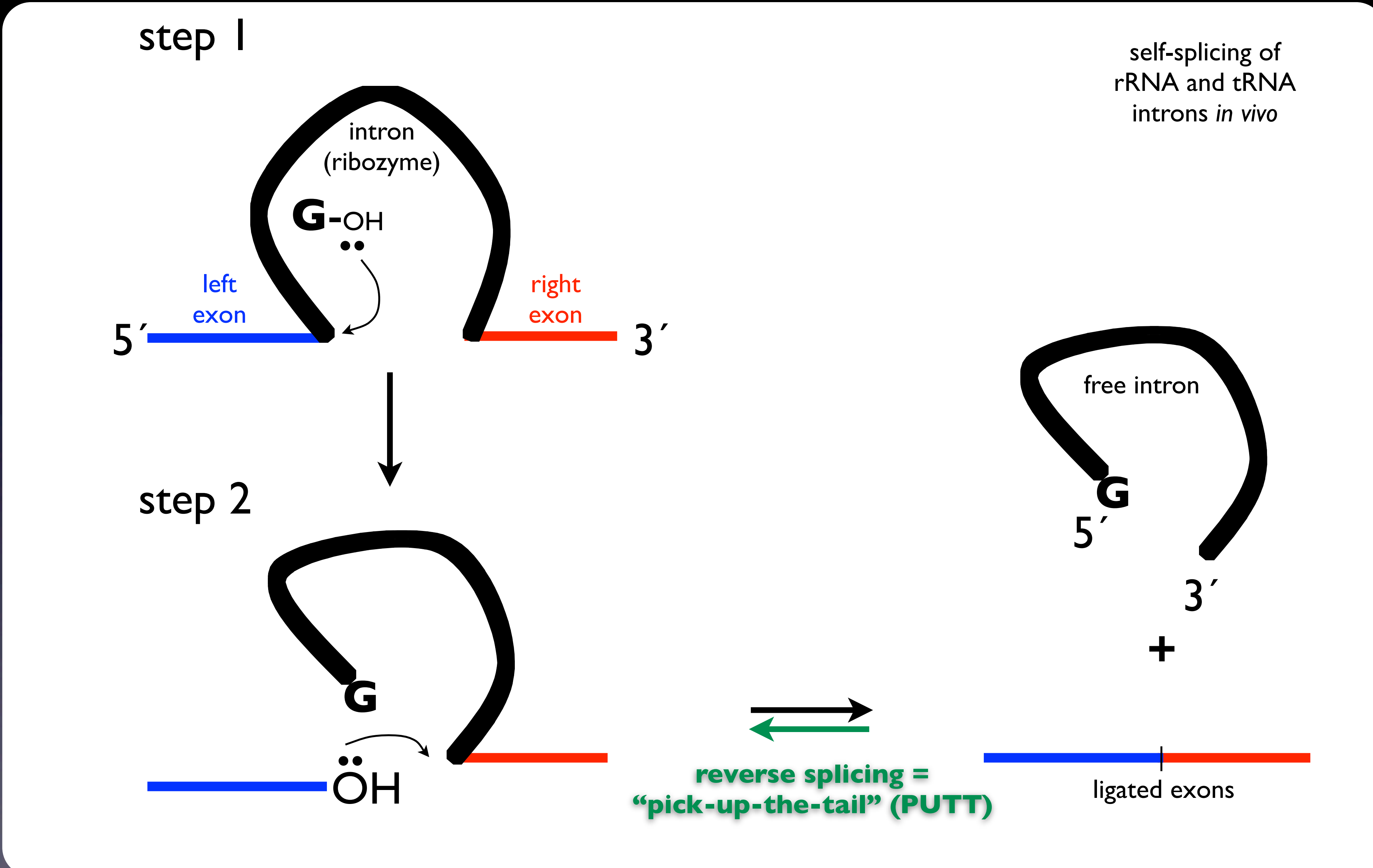
Lehman (2003) *J. Mol. Evol.* **56**, 770–777.

Lehman (2008) *Chem. Biodiver.* **5,** 1707–1717.

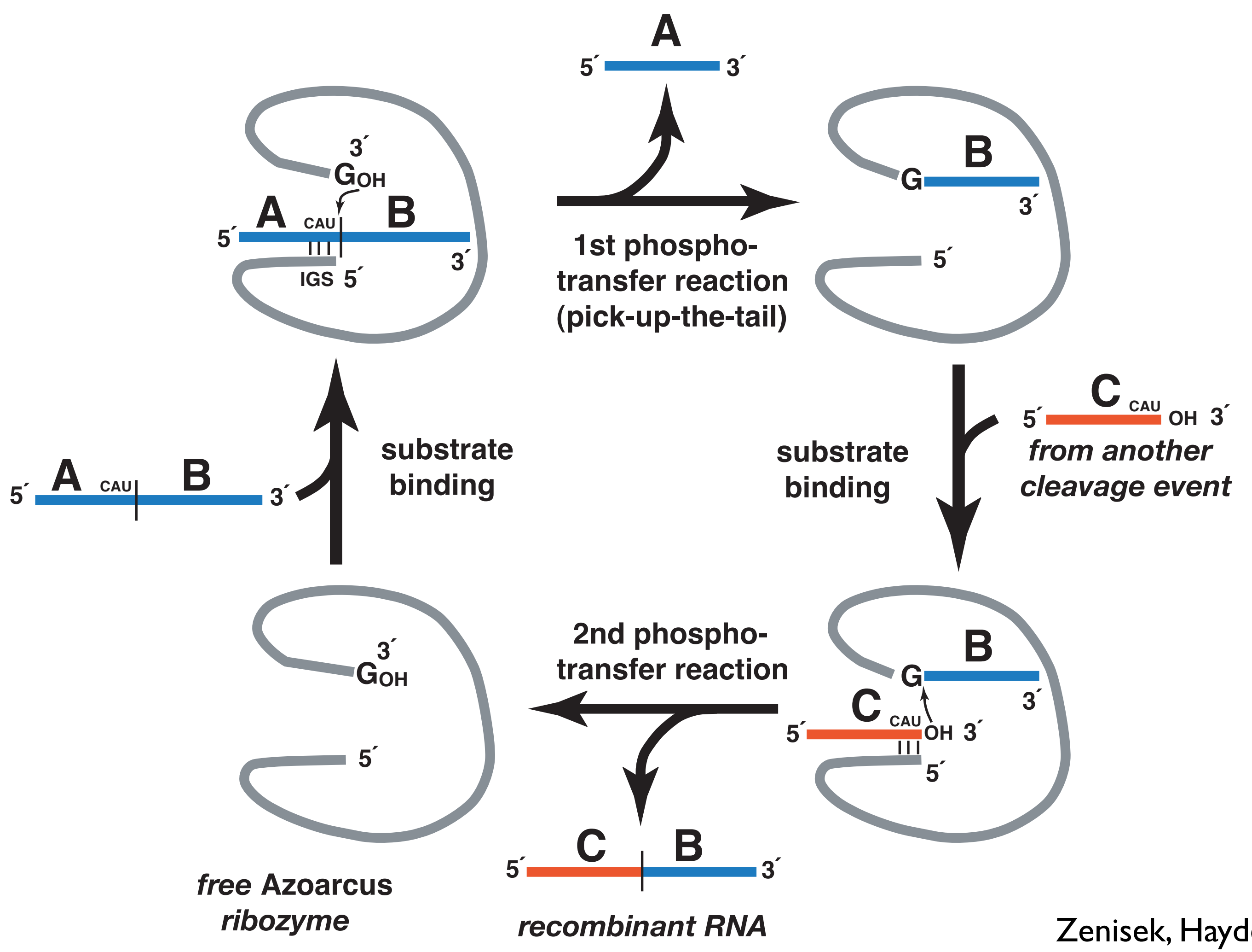
Lehman *et al.* (2011) *Entropy* **13,** 17–37.

Vaidya *et al.* (2012) *Nature* **490,** 72–77.

getting RNAs to recombine RNAs: group I introns do this in Nature

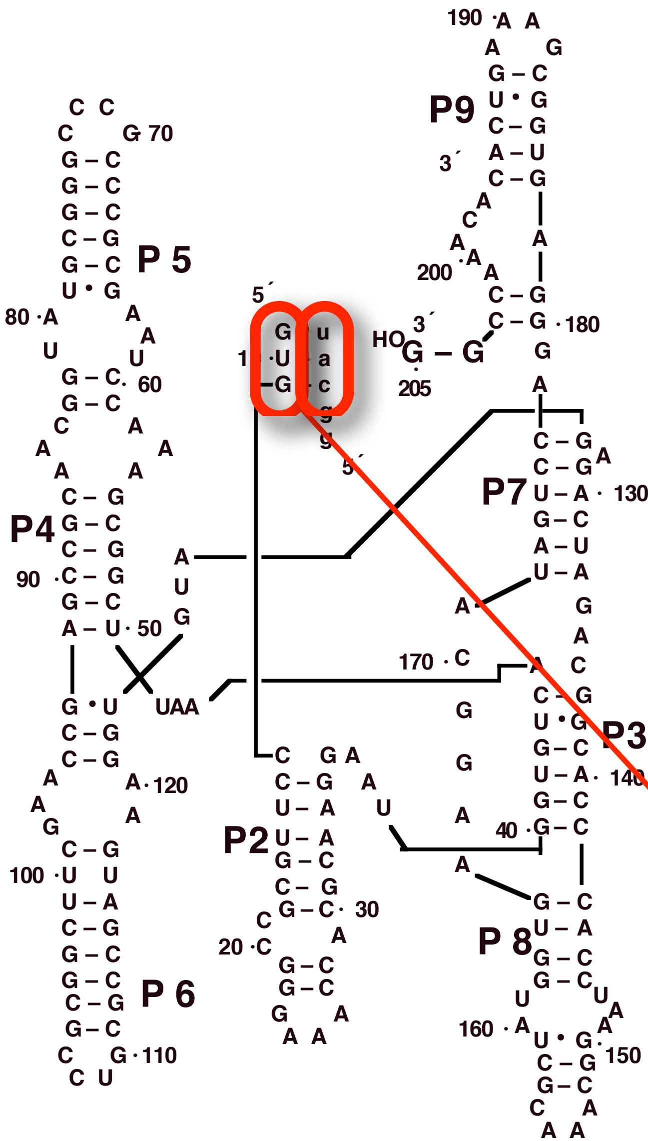


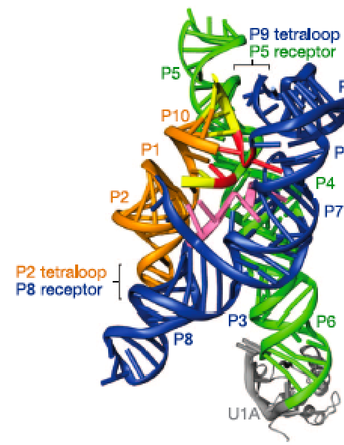
recombination scheme by group I ribozymes



Zenisek, Hayden & Lehman (2007) *Artif. Life* **13,** 279–289.

the *Azoarcus* ribozyme as a recombinase





self-splicing intron from the isoleucine tRNA of the purple bacterium *Azoarcus*

L–8 ribozyme is 197 nt long, and has a 71% G+C content

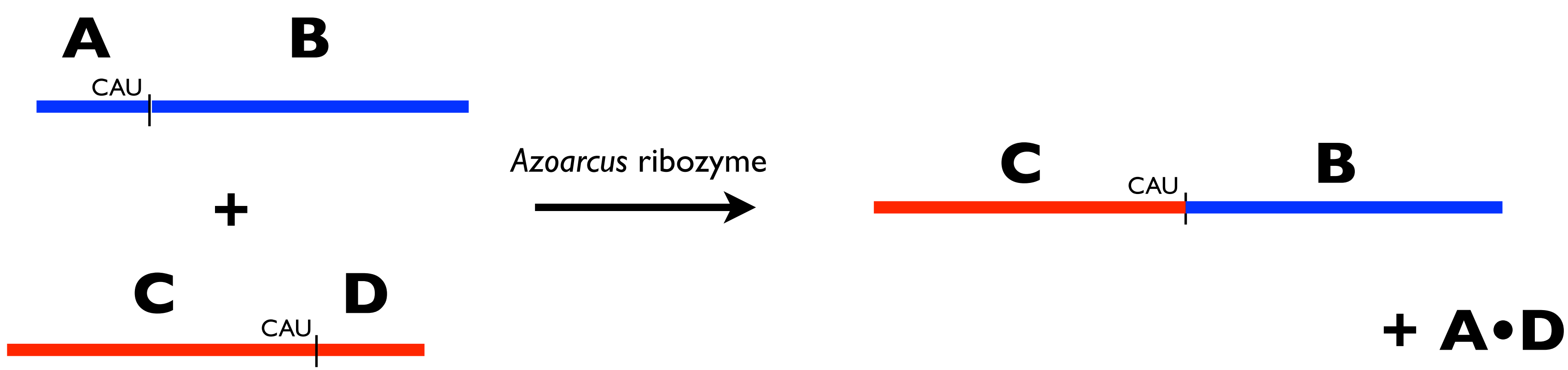
active up to 70°C

internal guide sequence is GUG, its complement (*i.e.*, "tag") is CAU

RNA-directed recombination of short oligomers

Azoarcus ribozyme: IGS = GUG; target = CAU

SNL-1a	GGCAU•AAAUAAAUAAAUAAAUA	22-mer
SNL-2a	GGAAAGGCAU•AAAUA	15-mer
SNL-4a	GGCAU•GGCCGAAACAGC	17-mer
SNL-5a	GGGAGUCUGAUGAGGCAU•AAAUA	23-mer
	"head" • "tail"	

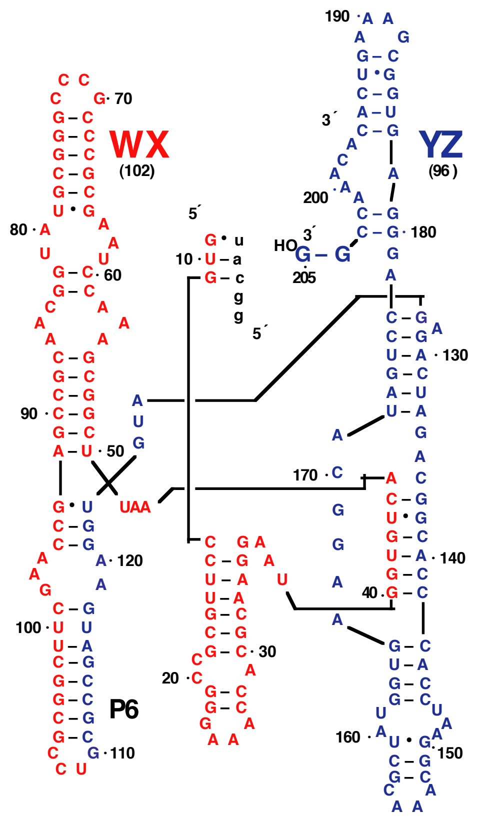


SNL-1a X SNL-2a: 22-mer + *15-mer ➔ *27-mer + 10-mer

recombining the recombinase itself

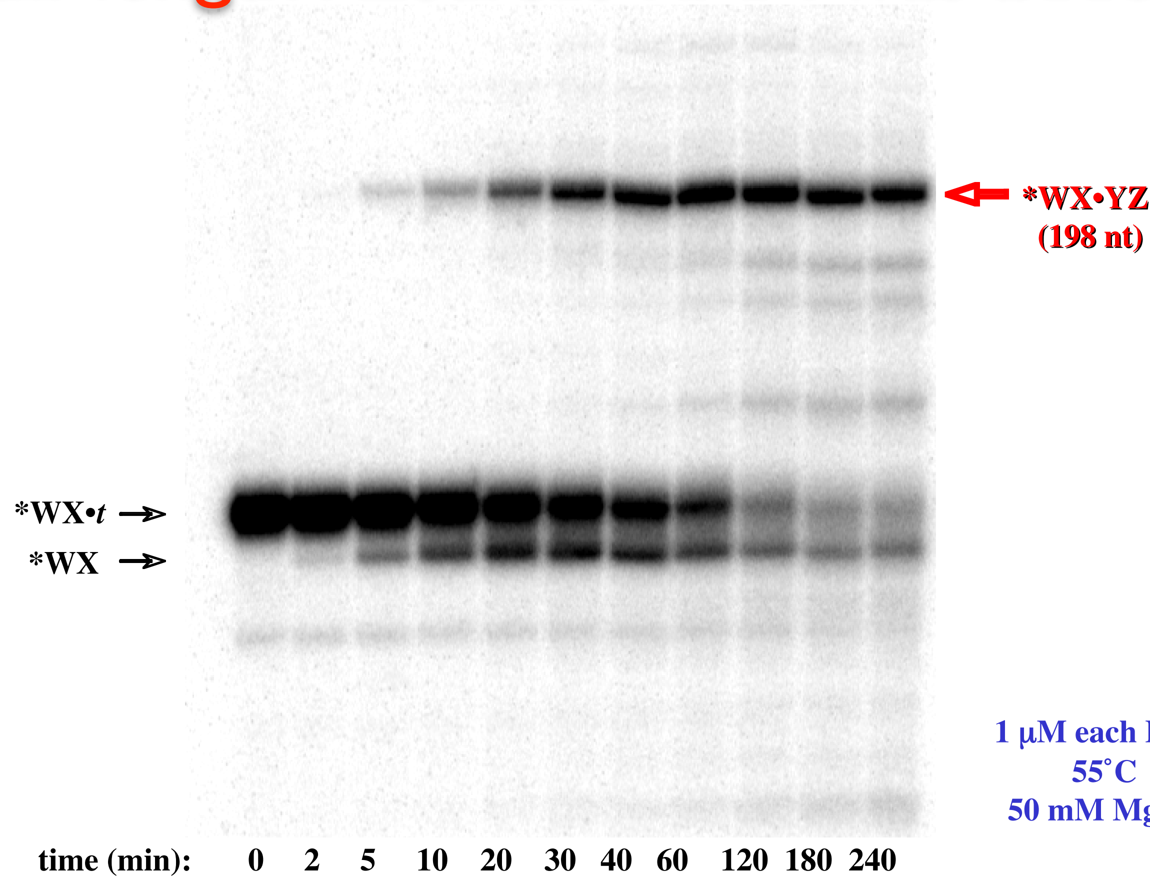
AZOARCUS RIBOZYME

198-nt *Azoarcus* ribozyme



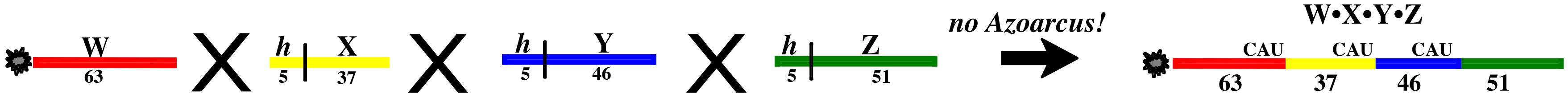
Azoarcus RCL6
"binary"

no full-length *Azoarcus* RNA was added!

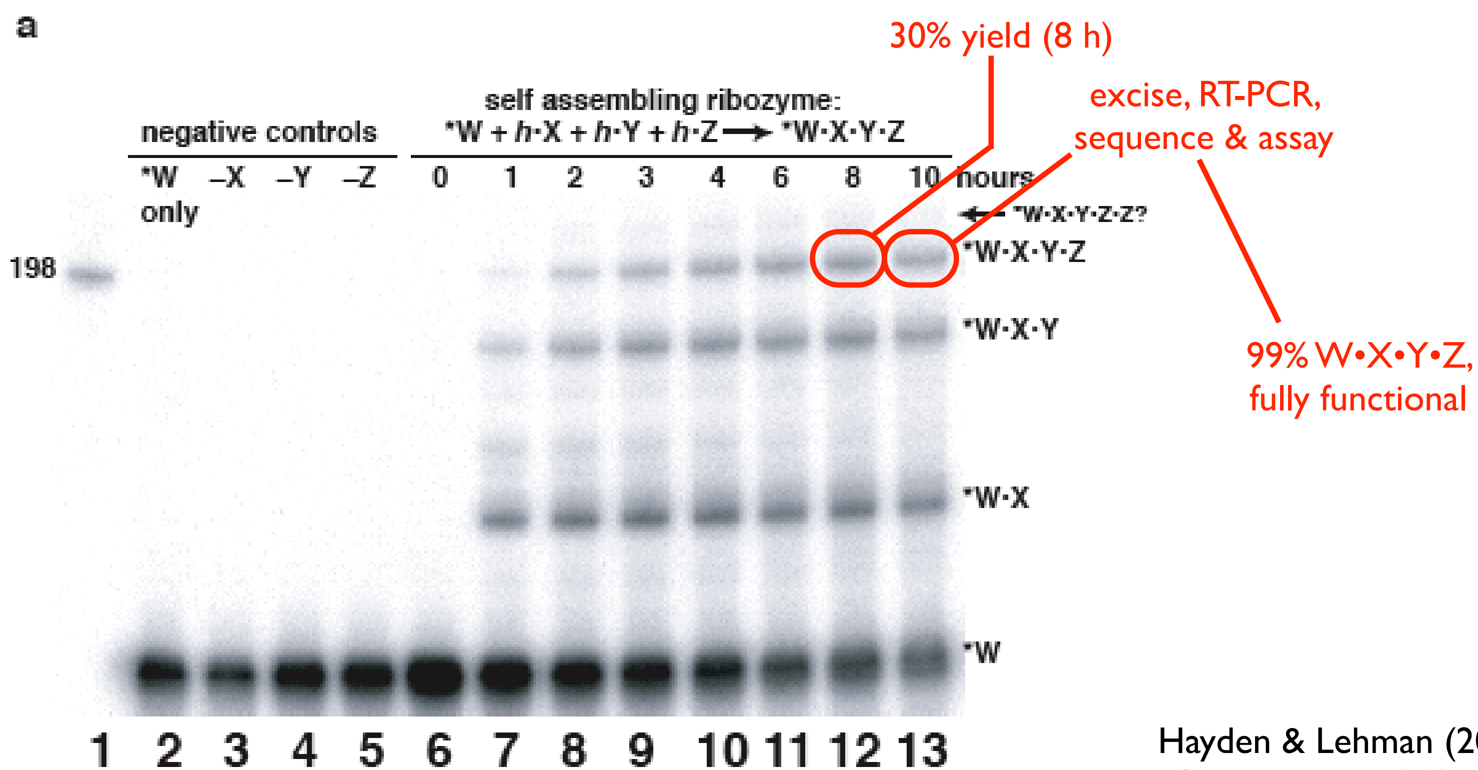


1 µM each RNA
55°C
50 mM $MgCl_2$

four-piece (quad) self-assembly

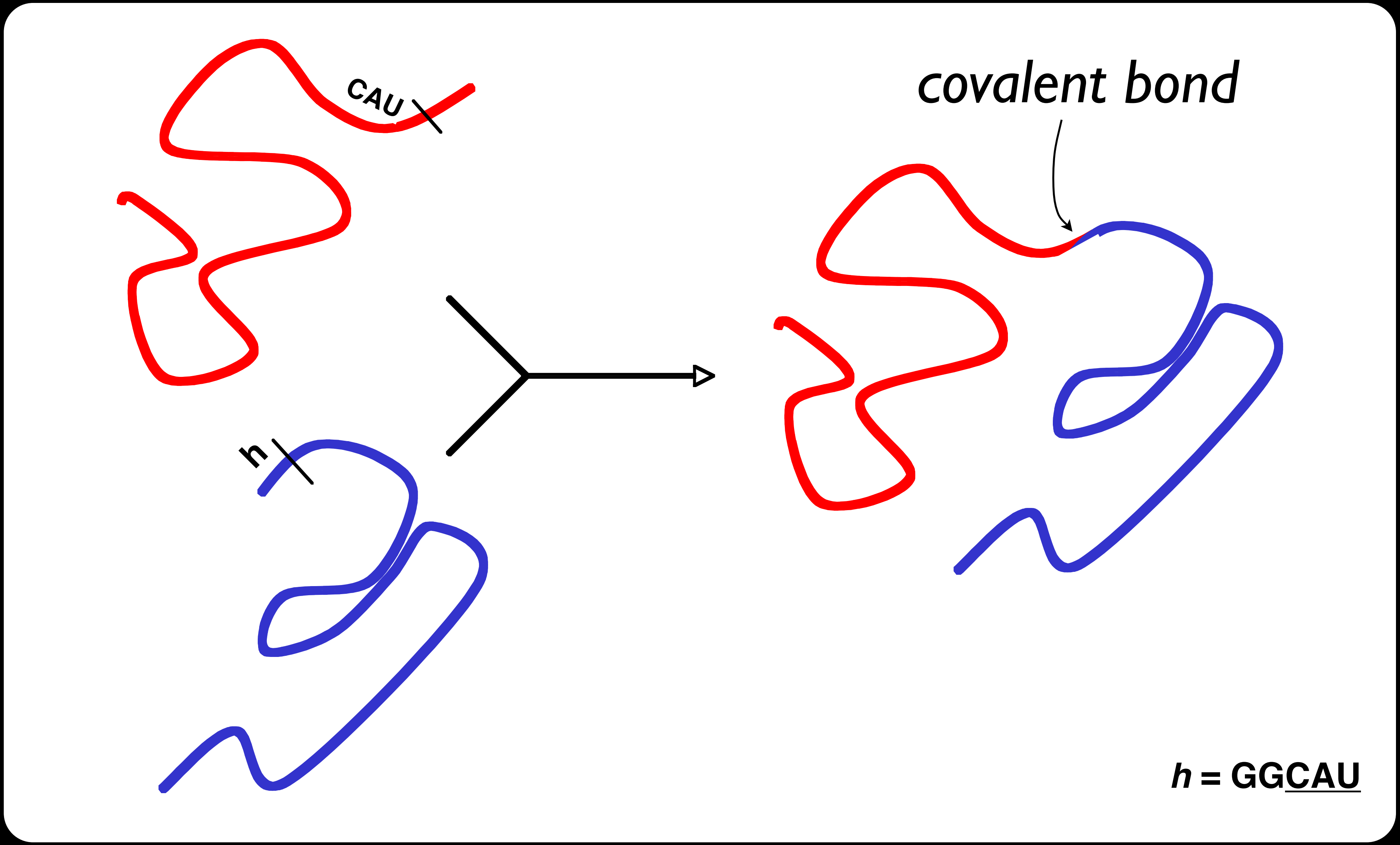


198-nt *Azoarcus* ribozyme

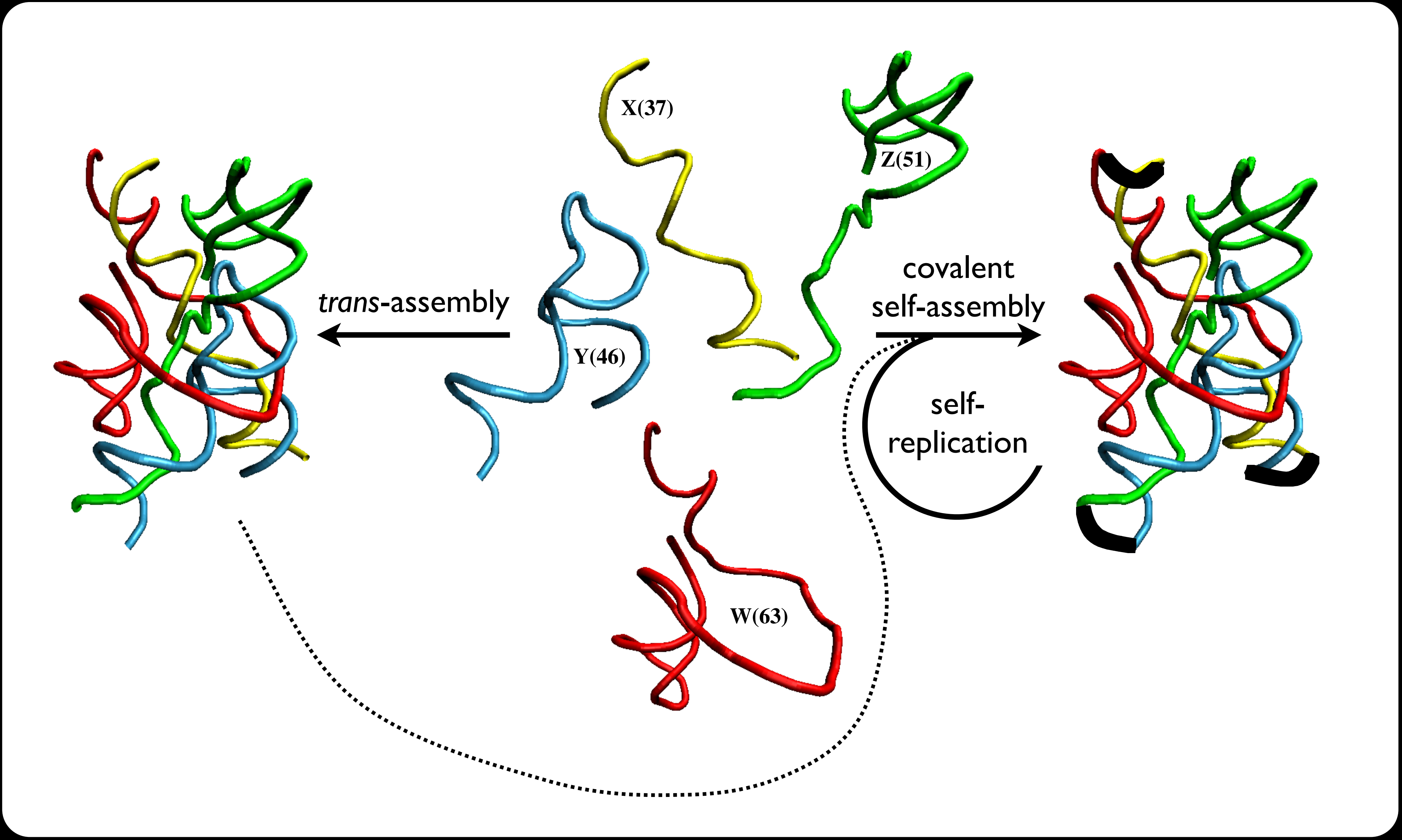


Hayden & Lehman (2006)
Chem. Biol. **13,** 909–918.

this is a “self-assembling” RNA



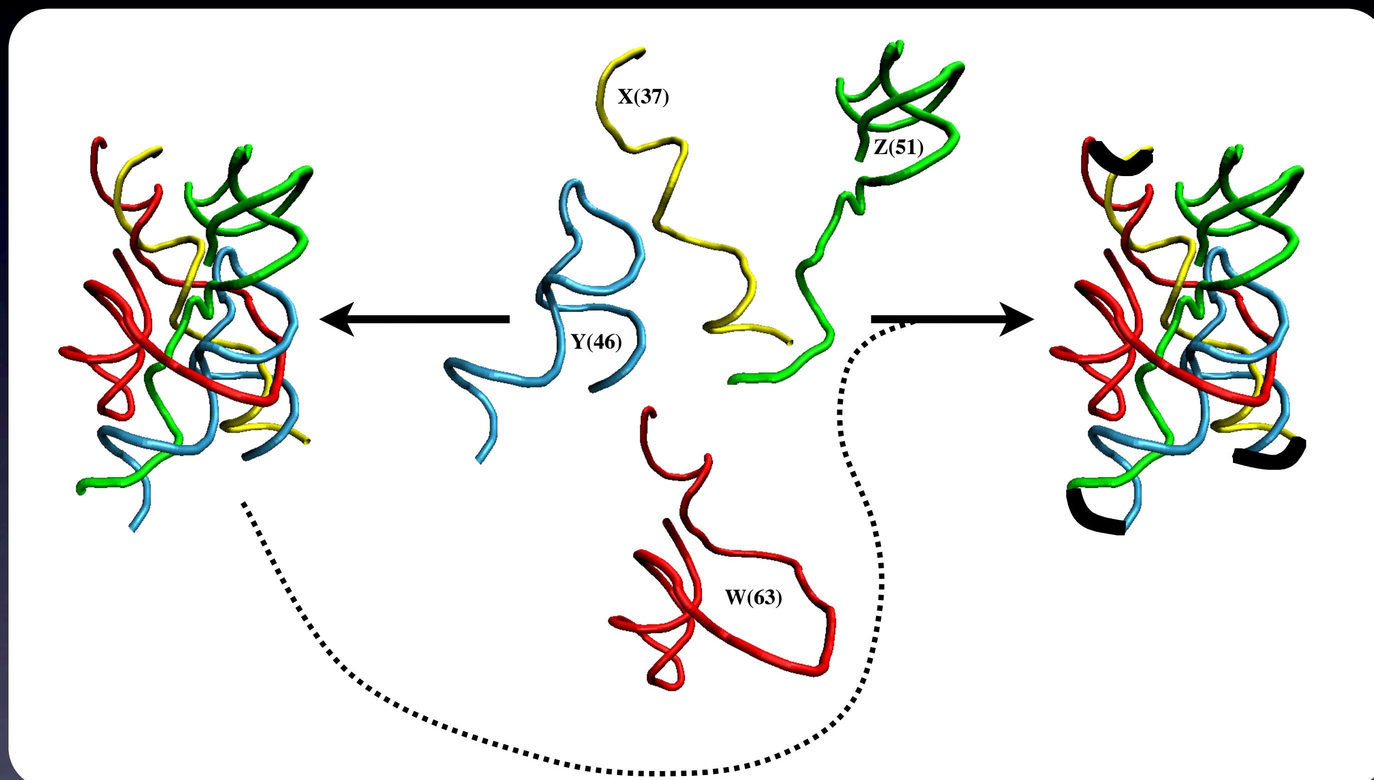
how? *trans*-catalysis first!

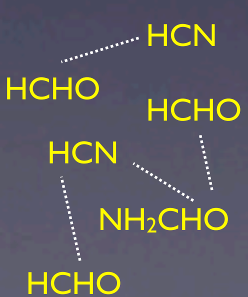


the concept of “self” requires a consideration of chemical bond strengths

hydrogen bond = –8 kJ/mol/H-bond

covalent bond = –22 kJ/mol/phosphodiester bond

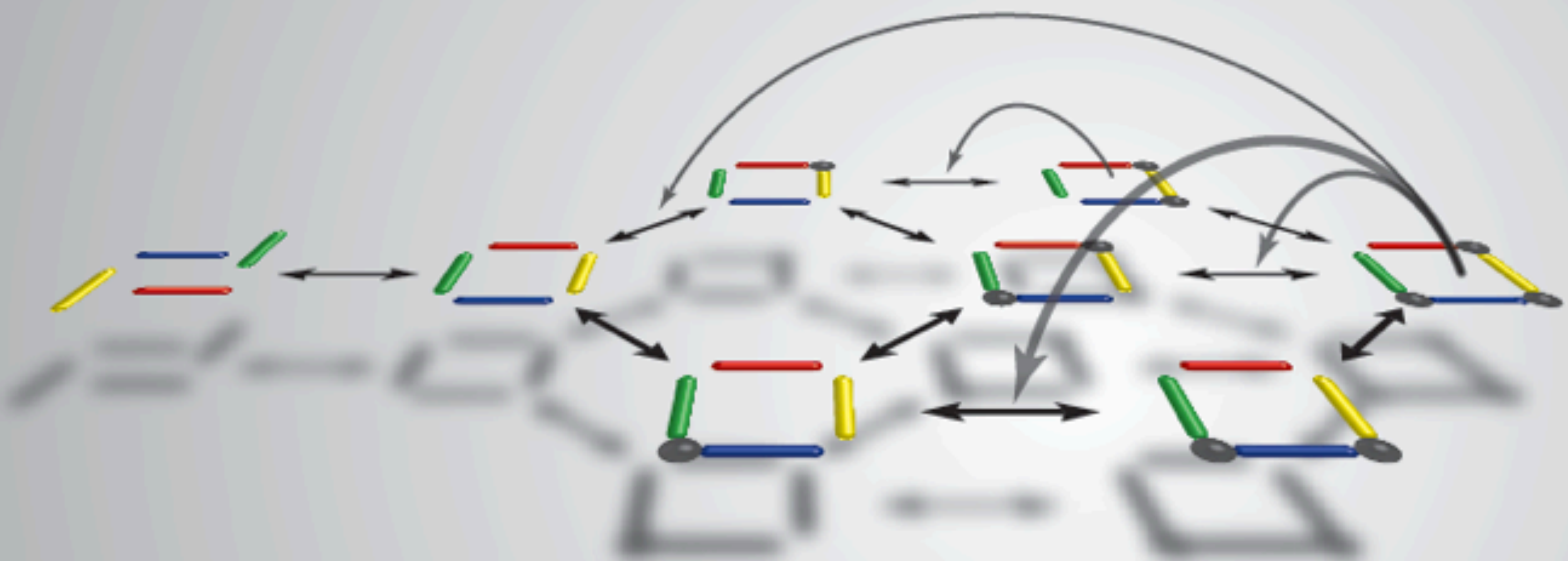




bond type gradient

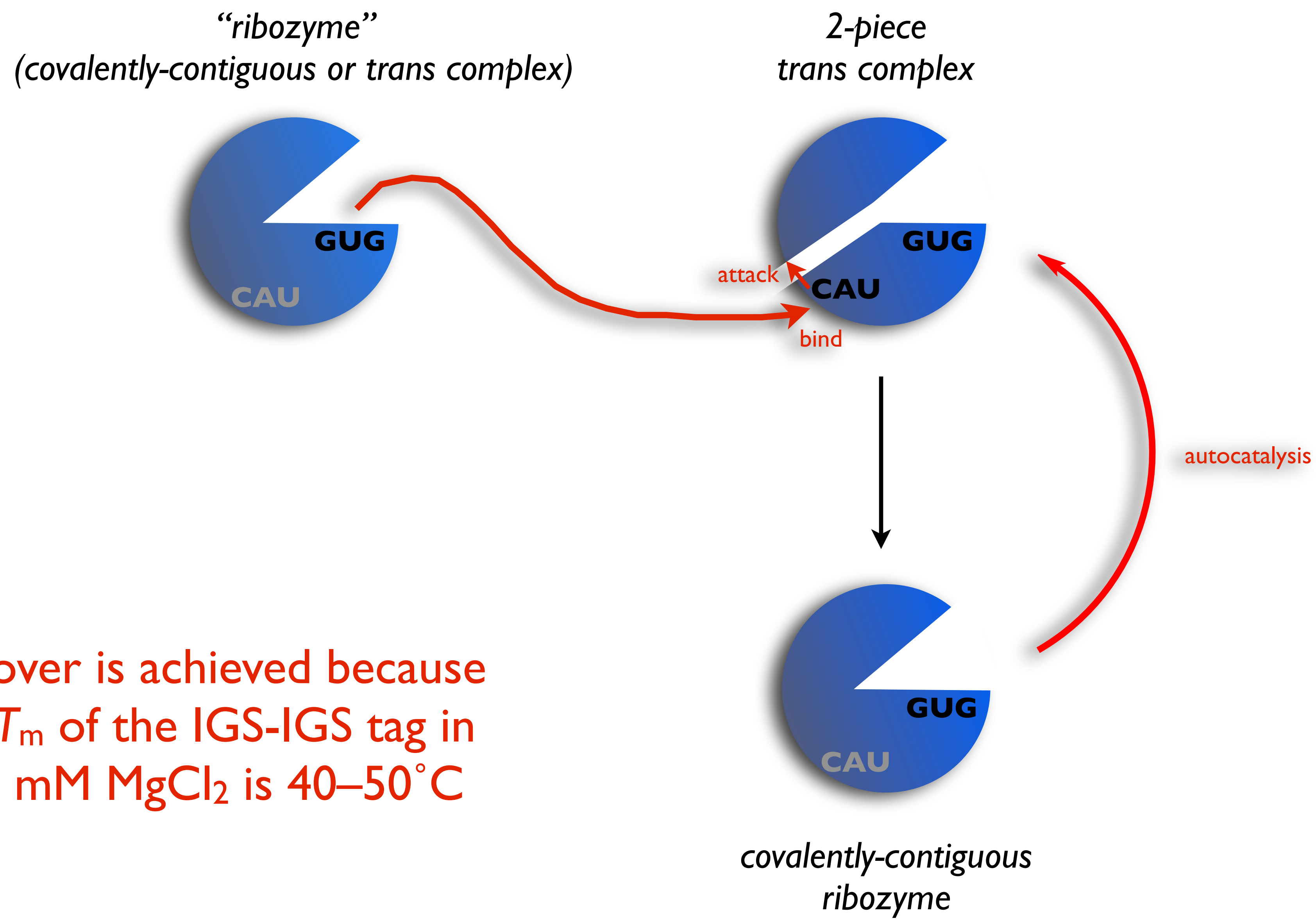
RNA

a small selfish (?) autocatalytic network



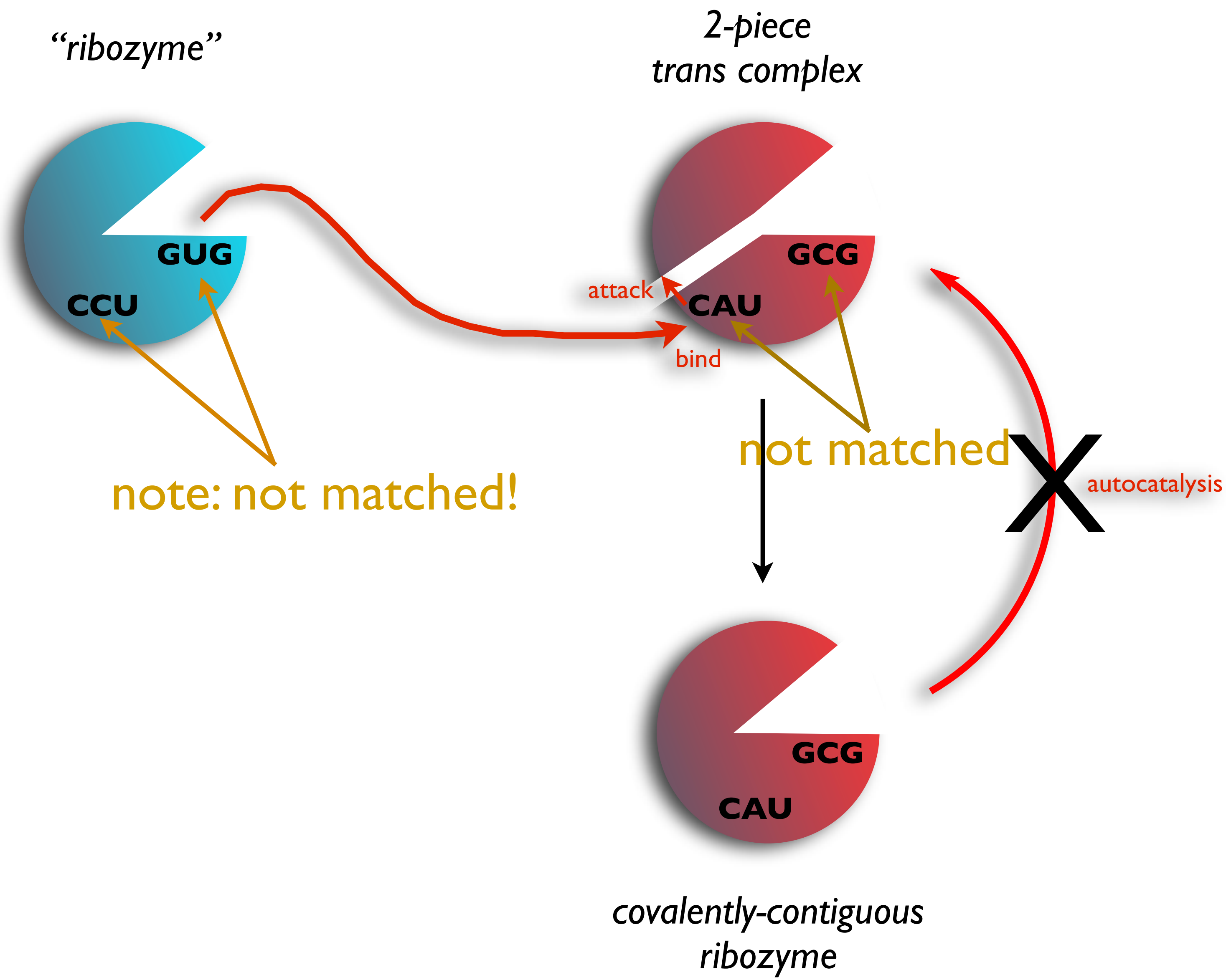
Hayden, von Kiedrowski, Lehman (2008)
Angew. Chem. Int. Ed. **47**, 8424–8428.

using information ...“selfishly”

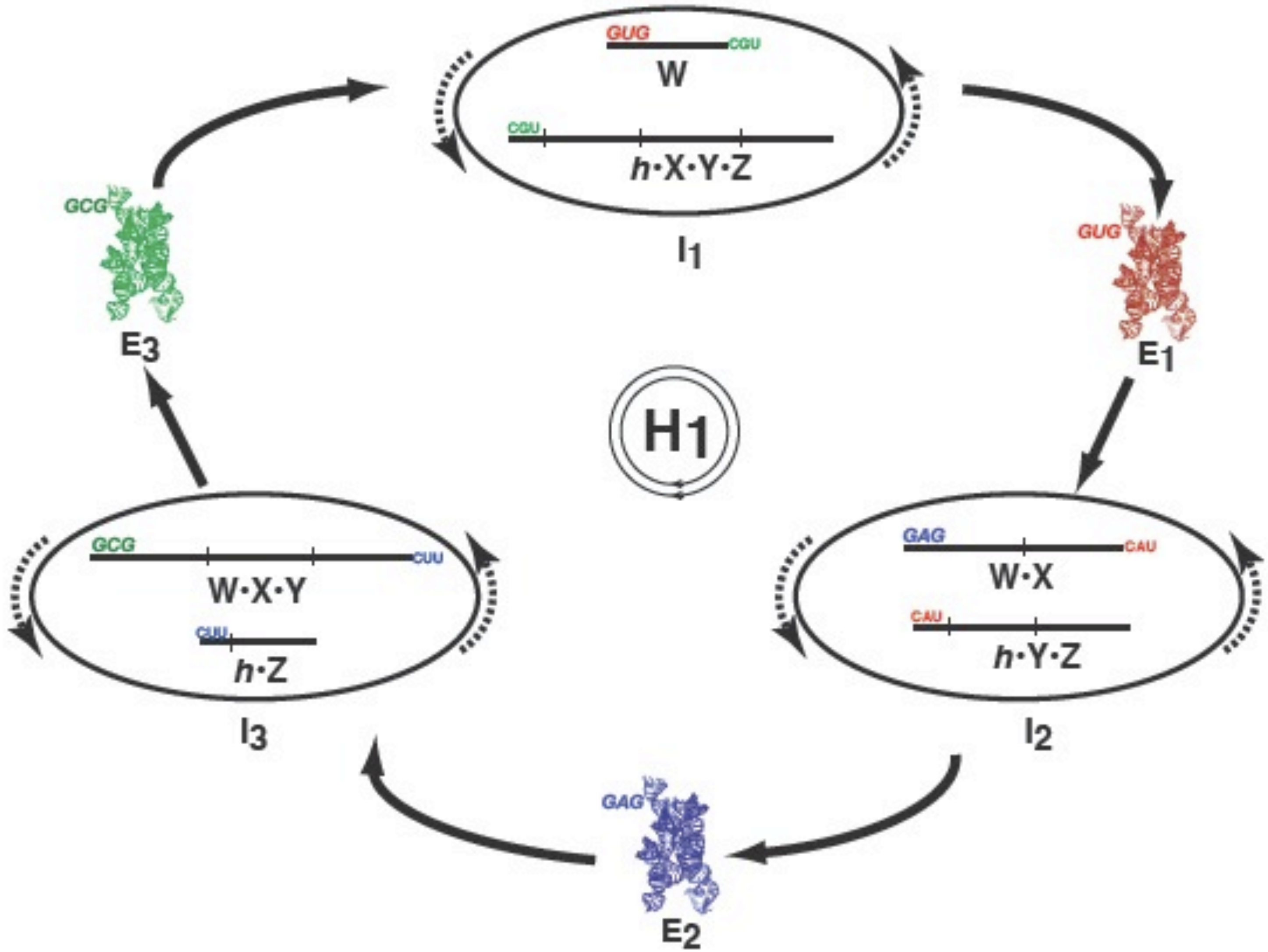


turnover is achieved because the T_m of the IGS-IGS tag in 100 mM $MgCl_2$ is 40–50˚C

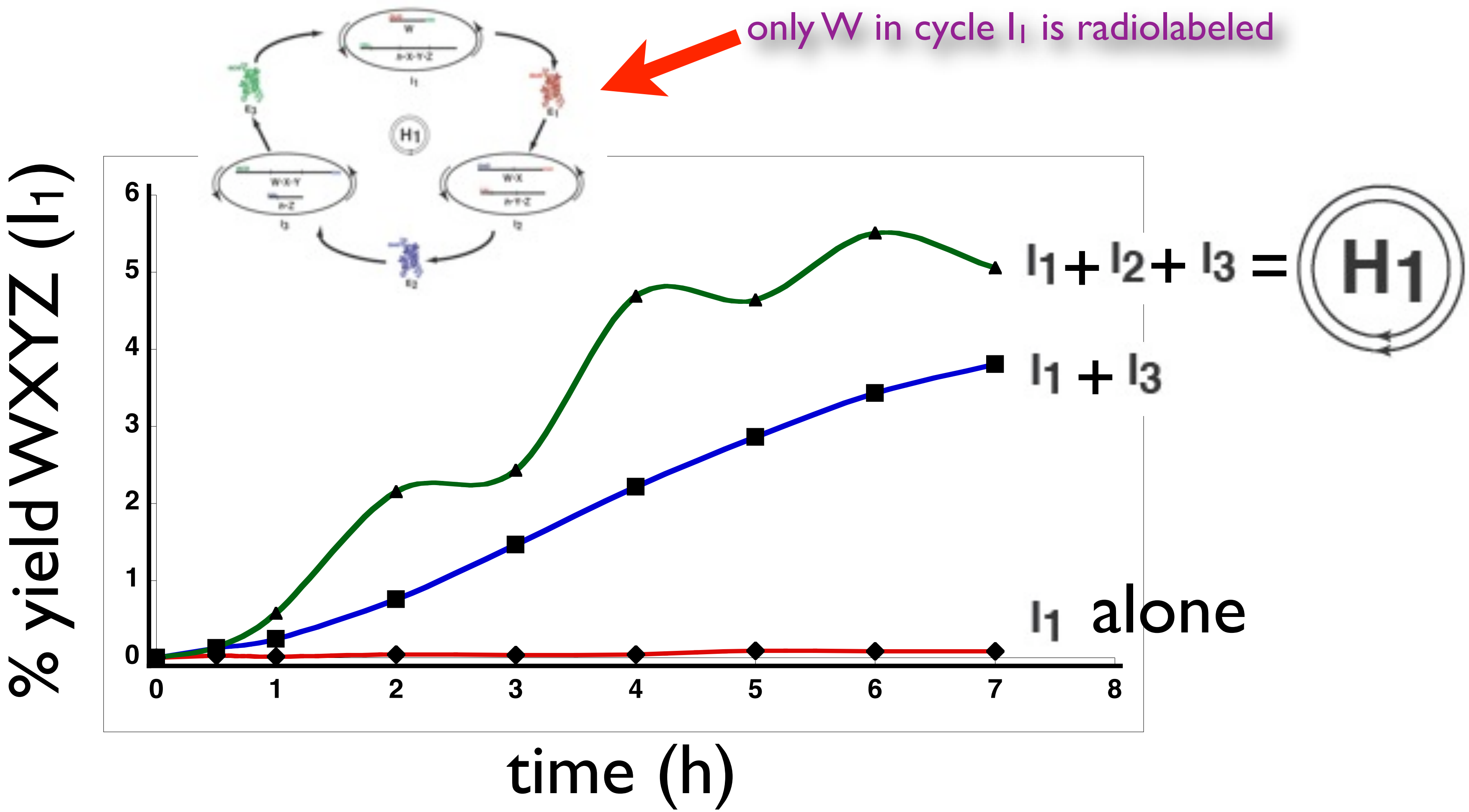
using information ...“cooperatively”?



a putative cooperative cycle



replicator yield is highest when all three components are present



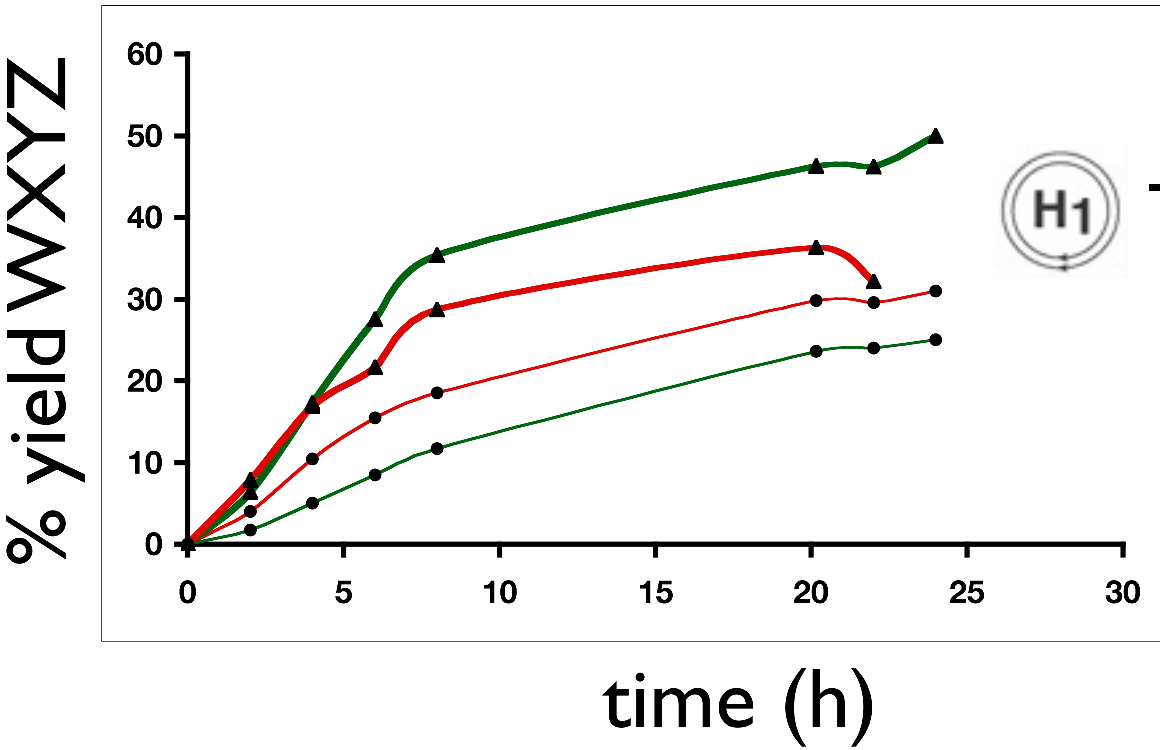
"closed" reaction

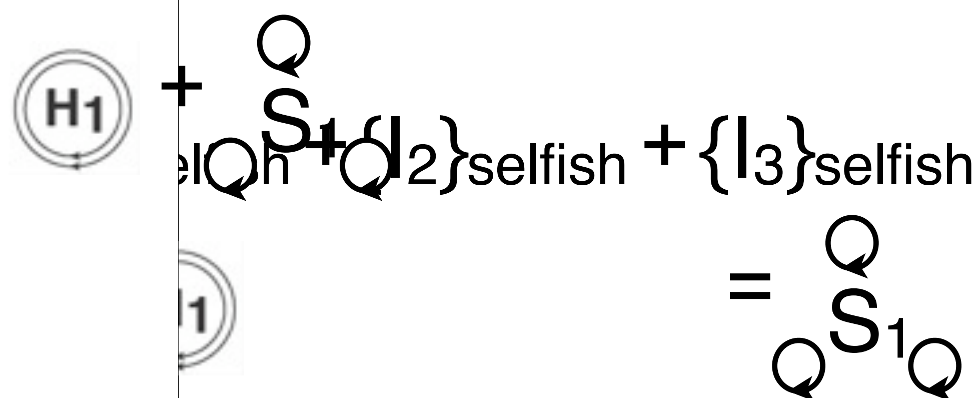
a competitive advantage to cooperation

the cooperative cycle out-competes the selfish replicators...

mismatched guides & tags

matched guides & tags

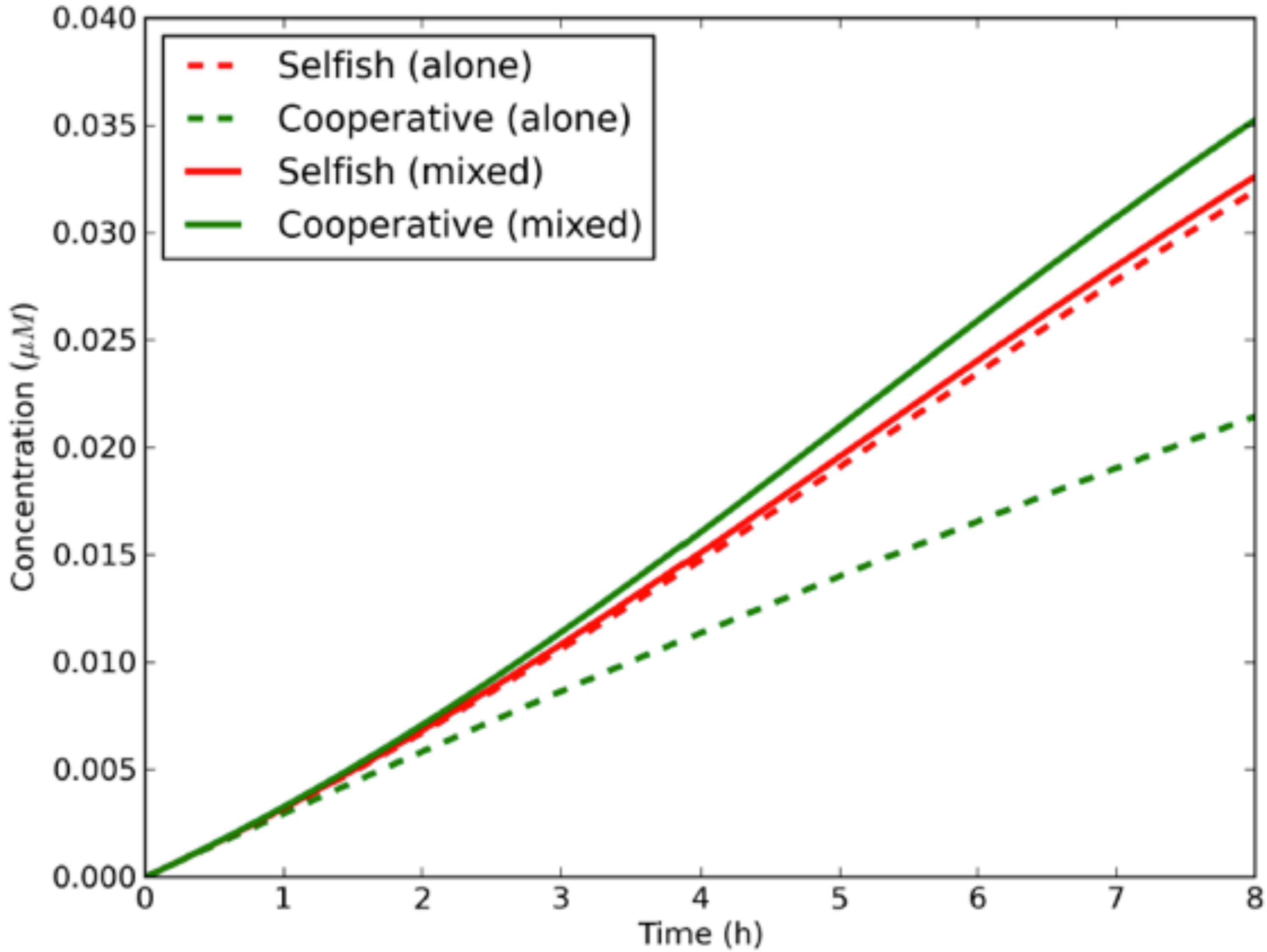




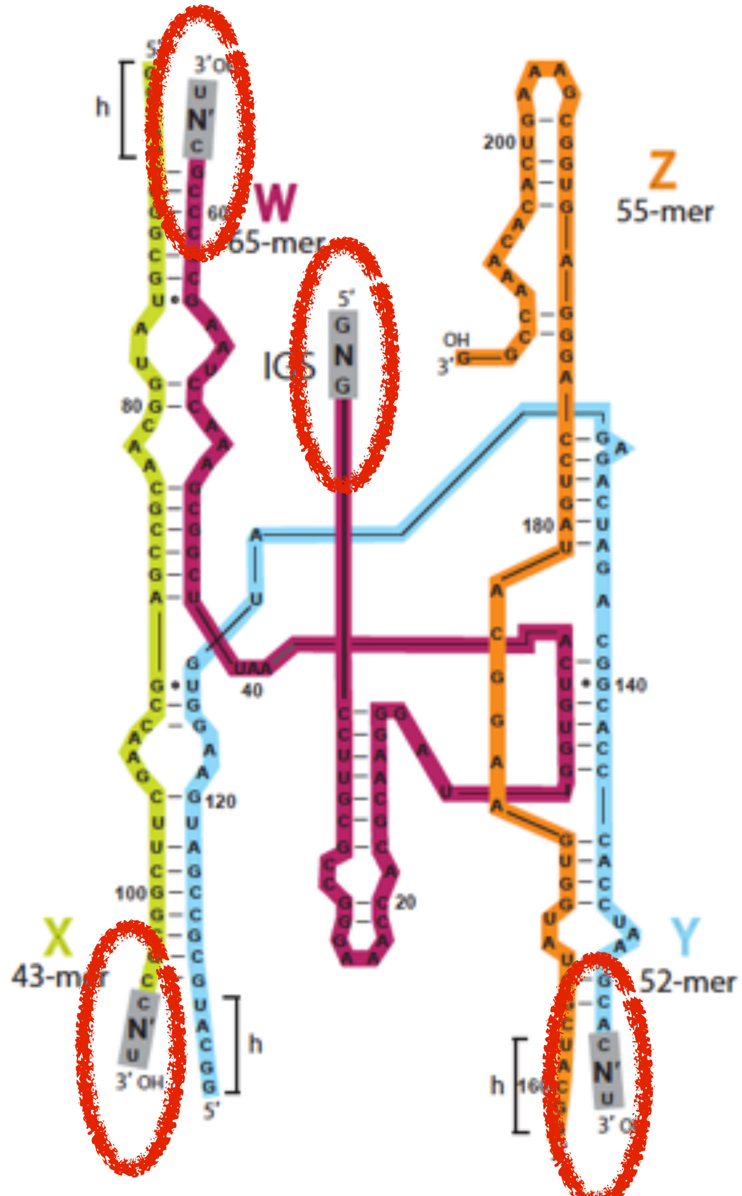
... but only when in mixed in the same population

Vaidya, Manapat, Chen, Xulvi-Brunet, Hayden, Lehman
(2012) *Nature* 490, 72–77.

mathematical modeling supports empirical data (Michael Manapat / Irene Chen)



moving beyond this single example: randomization experiment



GNG W CN′U

GNG W X CN′U

GNG W X Y CN′U

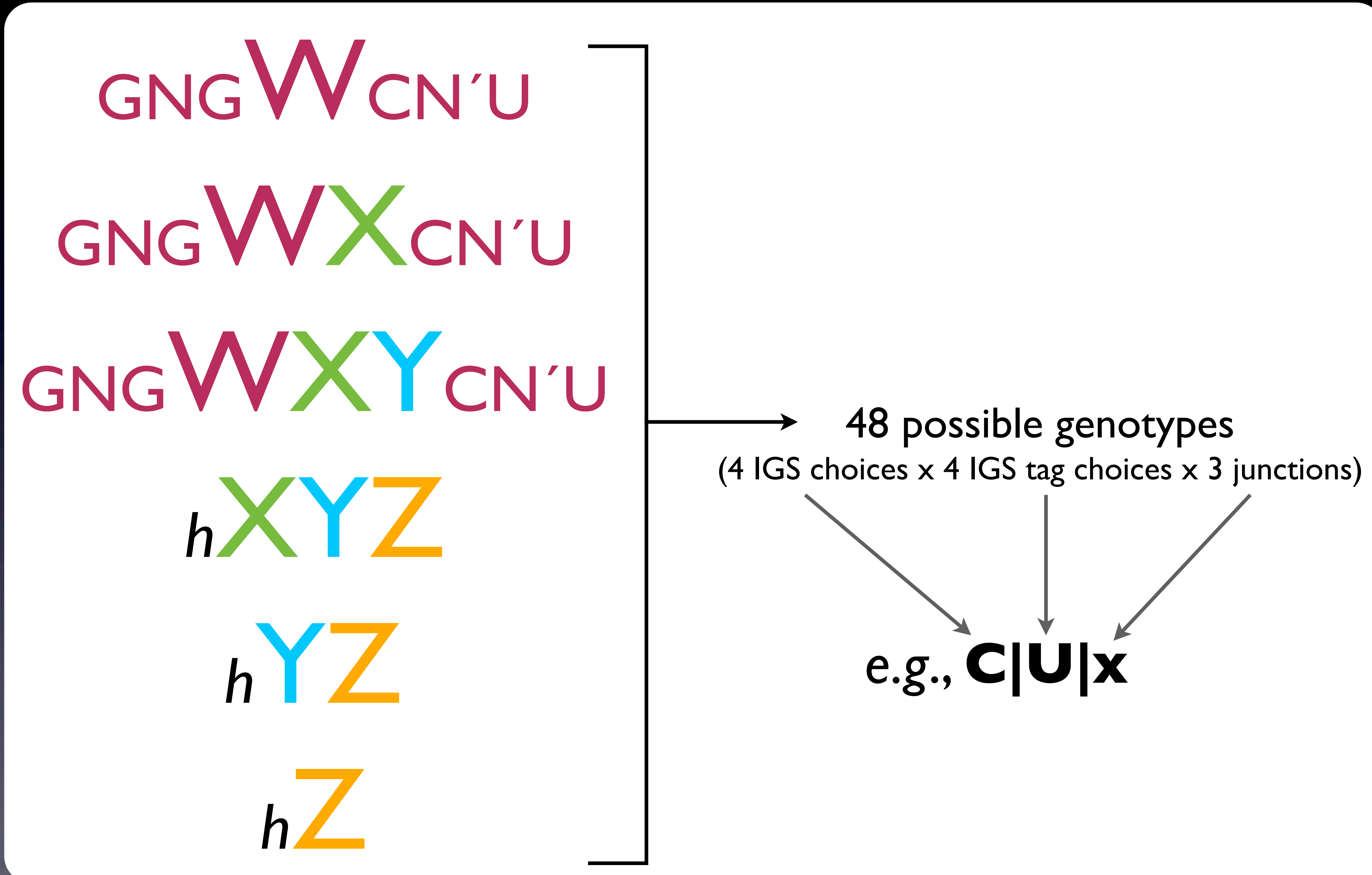
h X Y Z

h Y Z

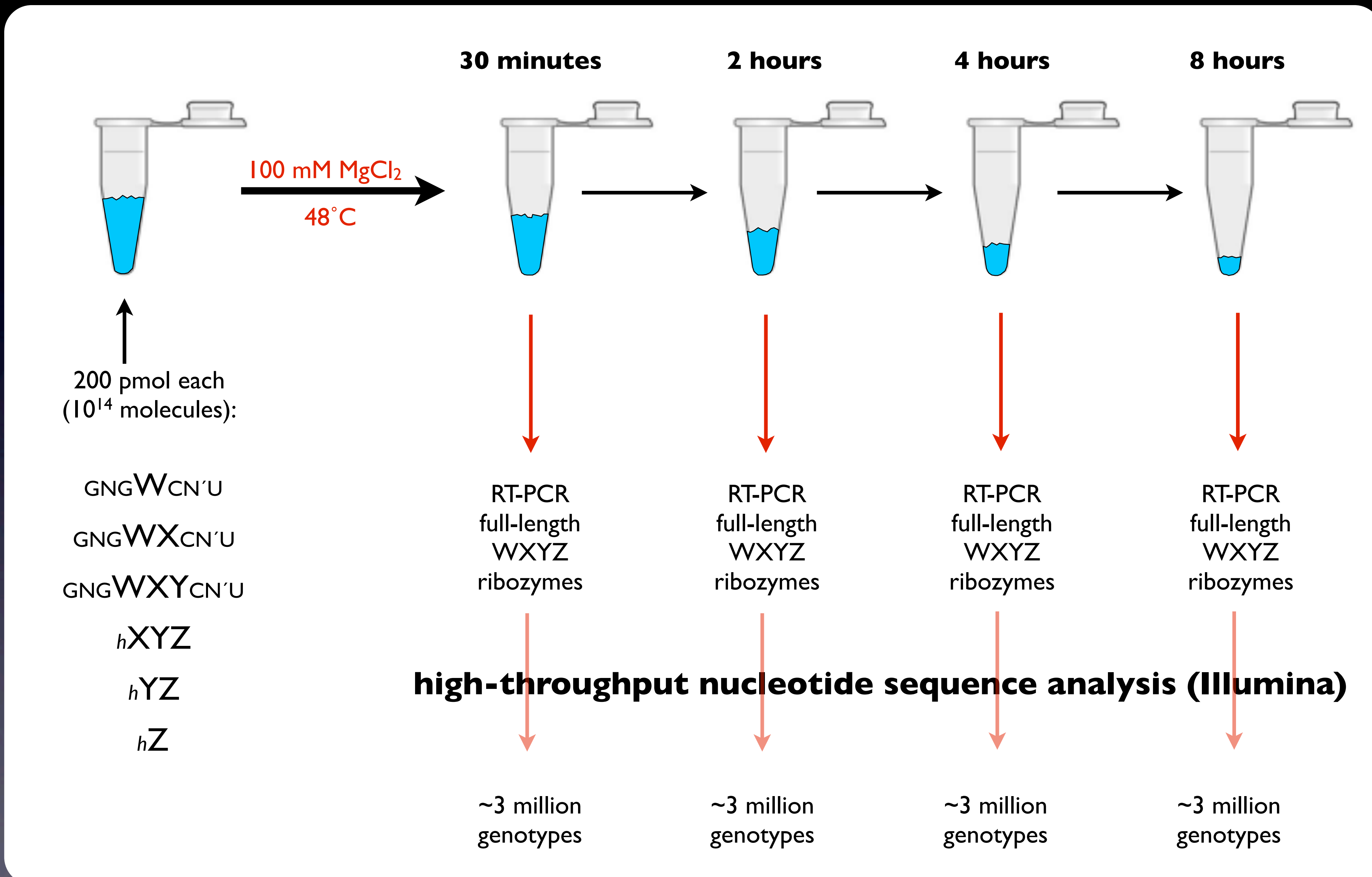
h Z

51 species

randomization experiment



randomization experiment



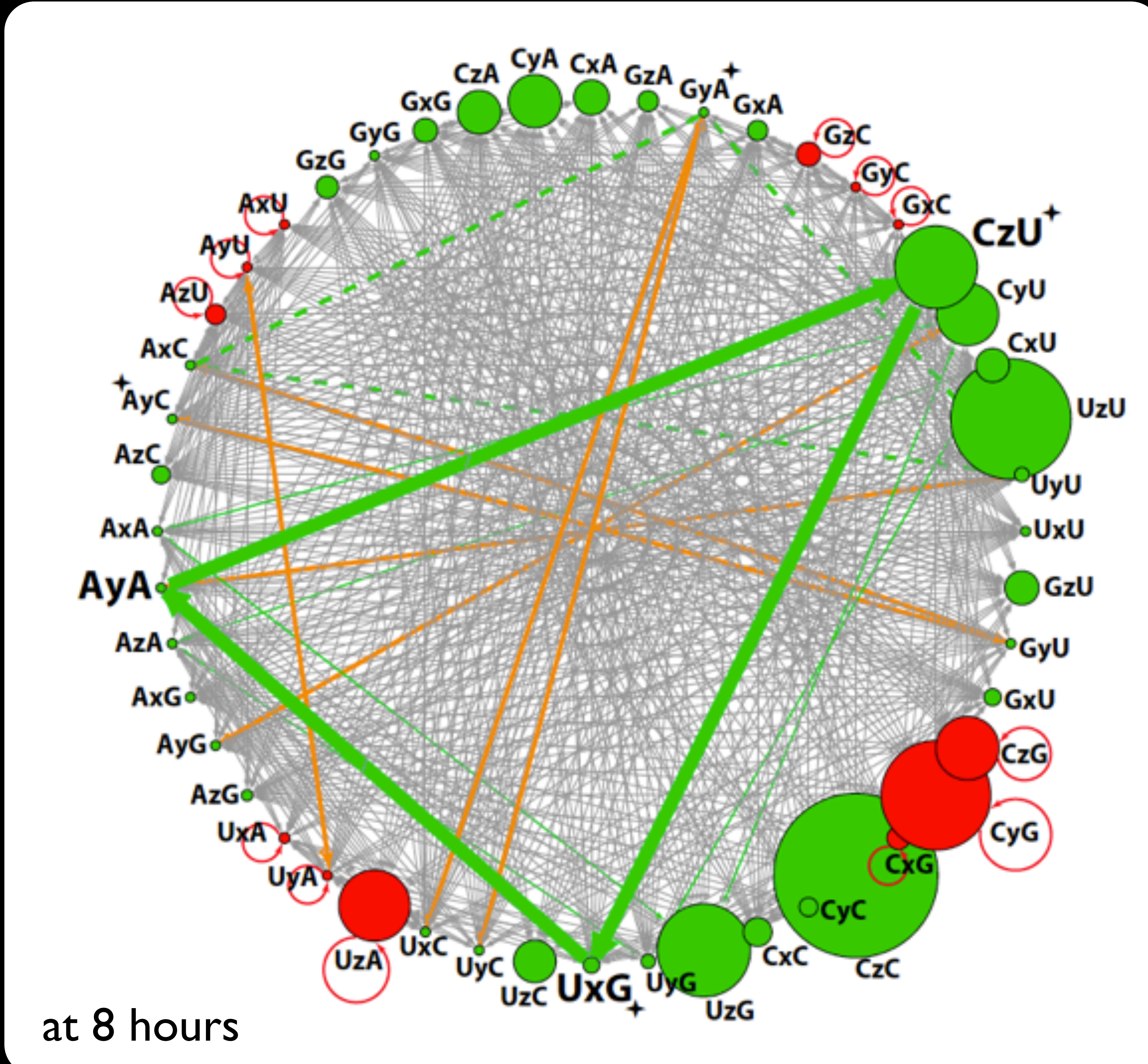
global visualization: results at 8 hr

red: autocatalysts

green: "cooperators"

orange: <u>both</u> members of 2MCs increasing over time

thick green: UGx + AAy + CUz



Vaidya, Manapat, Chen, Xulvi-Brunet, Hayden, Lehman (2012) *Nature* 490, 72–77.

Hamilton's Rule

$$rb > c$$

r = degree of relatedness between two genotypes;

b = additional reproductive benefit gained by the recipient of cooperative act

c = the reproductive cost incurred to the donor of the cooperative act

Game Theoretic Principles Manifested in RNA (IGS-Tag)

2-player games:

AA AA	AA AC	AA AG	AA AU	AC AA	AC AC	AC AG	AC AU	AG AA	AG AC	AG AG	AG AU	AU AA	AU AC	AU AG	AU AU
AA CA	AA CC	AA CG	AA CU	AC CA	AC CC	AC CG	AC CU	AG CA	AG CC	AG CG	AG CU	AU CA	AU CC	AU CG	AU CU
AA GA	AA GC	AA GG	AA GU	AC GA	AC GC	AC GG	AC GU	AG GA	AG GC	AG GG	AG GU	AU GA	AU GC	AU GG	AU GU
AA UA	AA UC	AA UG	AA UU	AC UA	AC UC	AC UG	AC UU	AG UA	AG UC	AG UG	AG UU	AU UA	AU UC	AU UG	AU UU
CA AA	CA AC	CA AG	CA AU	CC AA	CC AC	CC AG	CC AU	CG AA	CG AC	CG AG	CG AU	CU AA	CU AC	CU AG	CU AU
CA CA	CA CC	CA CG	CA CU	CC CA	CC CC	CC CG	CC CU	CG CA	CG CC	CG CG	CG CU	CU CA	CU CC	CU CG	CU CU
CA GA	CA GC	CA GG	CA GU	CC GA	CC GC	CC GG	CC GU	CG GA	CG GC	CG GG	CG GU	CU GA	CU GC	CU GG	CU GU
CA UA	CA UC	CA UG	CA UU	CC UA	CC UC	CC UG	CC UU	CG UA	CG UC	CG UG	CG UU	CU UA	CU UC	CU UG	CU UU
GA AA	GA AC	GA AG	GA AU	GC AA	GC AC	GC AG	GC AU	GG AA	GG AC	GG AG	GG AU	GU AA	GU AC	GU AG	GU AU
GA CA	GA CC	GA CG	GA CU	GC CA	GC CC	GC CG	GC CU	GG CA	GG CC	GG CG	GG CU	GU CA	GU CC	GU CG	GU CU
GA GA	GA GC	GA GG	GA GU	GC GA	GC GC	GC GG	GC GU	GG GA	GG GC	GG GG	GG GU	GU GA	GU GC	GU GG	GU GU
GA UA	GA UC	GA UG	GA UU	GC UA	GC UC	GC UG	GC UU	GG UA	GG UC	GG UG	GG UU	GU UA	GU UC	GU UG	GU UU
UA AA	UA AC	UA AG	UA AU	UC AA	UC AC	UC AG	UC AU	UG AA	UG AC	UG AG	UG AU	UU AA	UU AC	UU AG	UU AU
UA CA	UA CC	UA CG	UA CU	UC CA	UC CC	UC CG	UC CU	UG CA	UG CC	UG CG	UG CU	UU CA	UU CC	UU CG	UU CU
UA GA	UA GC	UAGG	UA GU	UC GA	UC GC	UC GG	UC GU	UG GA	UG GC	UG GG	UG GU	UU GA	UU GC	UU GG	UU GU
UA UA	UA UC	UA UG	UA UU	UC UA	UC UC	UC UG	UC UU	UG UA	UG UC	UG UG	UG UU	UU UA	UU UC	UU UG	UU UU

A self-assembles
B self-assembles
A assembles B
B assembles A

A assembles B A self-assemble
A assembles B B self-assemble

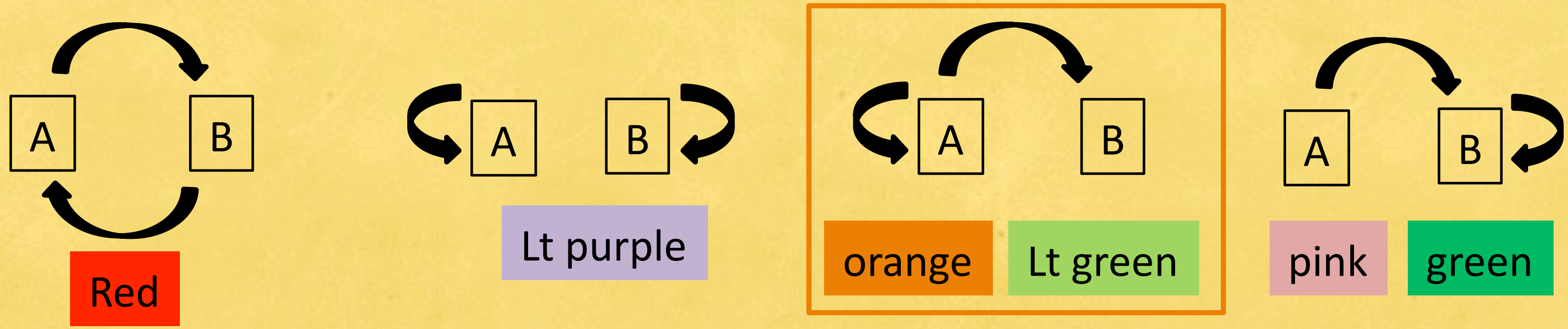
B assembles A A self-assemble
B assembles A B self-assemble

A assembles B B assembles A ALL assemble

A self-assemble B self-assemble ALL self-assemble

ALL assemble ALL SA ALL SA & ALL ASSEMBLE

Strategies:



Snowdrift game:

GC	AU	GU	CA	AG	CU	GG

Game 1: AU vs. CU

Game 2: GC vs. GG

Game 3: GC vs. AG

Game Theoretic Principles Manifested in RNA (IGS-Tag)

Game 1 payoff matrices:

General payoff matrix

	A	B
A	α	β
B	ψ	δ

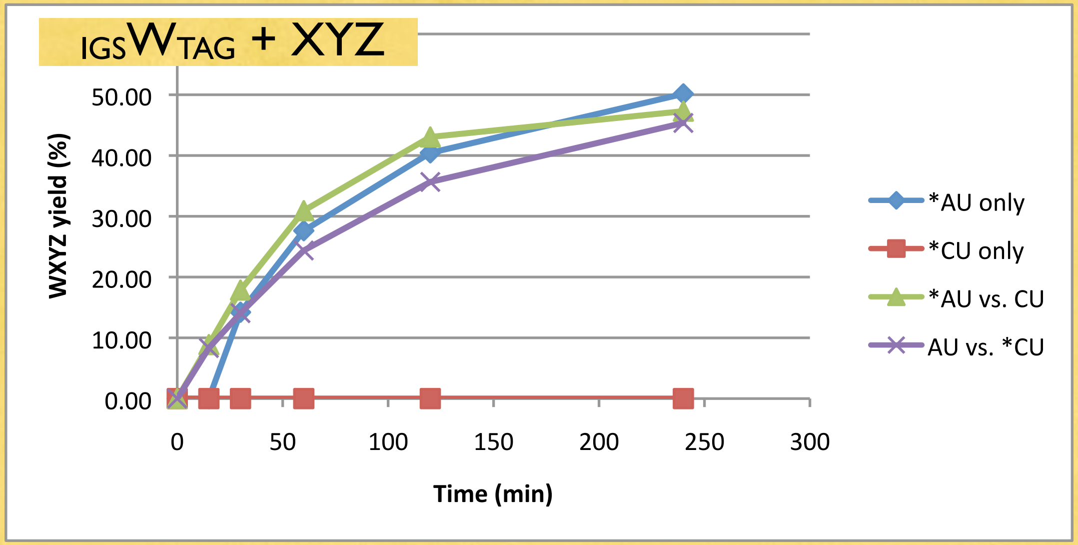
Snowdrift payoff matrix

	Cooperate	Defect
Cooperate	*b - c/2*	*b - c*
Defect	*b*	0

game 1: strategy A is the genotype with the GAU IGS and the CUU tag, while strategy 2 is the genotype with the GCU IGS and the CUU tag.

measured payoff matrix at 60 min:

6.9 pmol	7.7 pmol
6.1 pmol	0 pmol



at 60 min, there is no cost to cooperating, and the altruism of A is not penalized

in this experiment, α > ψ, and β > δ, meaning that A is always the dominant strategy; not snowdrift!

Nowak, M. A. (2006) *Evolutionary Dynamics: Exploring the Equations of Life* (Harvard Univ. Press, 2006).

putting it all together

- group I introns can be engineered to be general RNA recombinase enzymes
- the *Azoarcus* ribozyme can covalently self-assemble through recombination
- autocatalytic self-replication can occur in this system
- upon selection a temporal progression can be seen:
  1. autocatalysts
  2. simple 2-membered cooperative cycles
  3. 3-membered networks
  4. more complex networks?

there seems to be a simple mechanism by which networks can expand by being more efficient replicators than selfish autocatalysts

acknowledgements

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Dr. **Michael Manapat** (Harvard, now Google)
Dr. **Ramon Xulvi-Brunet** (Harvard)

"NilesH"

National Aeronautics
and Space Administration