Statistical Physics of Self-Replication

Review of paper by Jeremy England

Mobolaji Williams — Shakhnovich Journal Club — Nov. 18, 2016

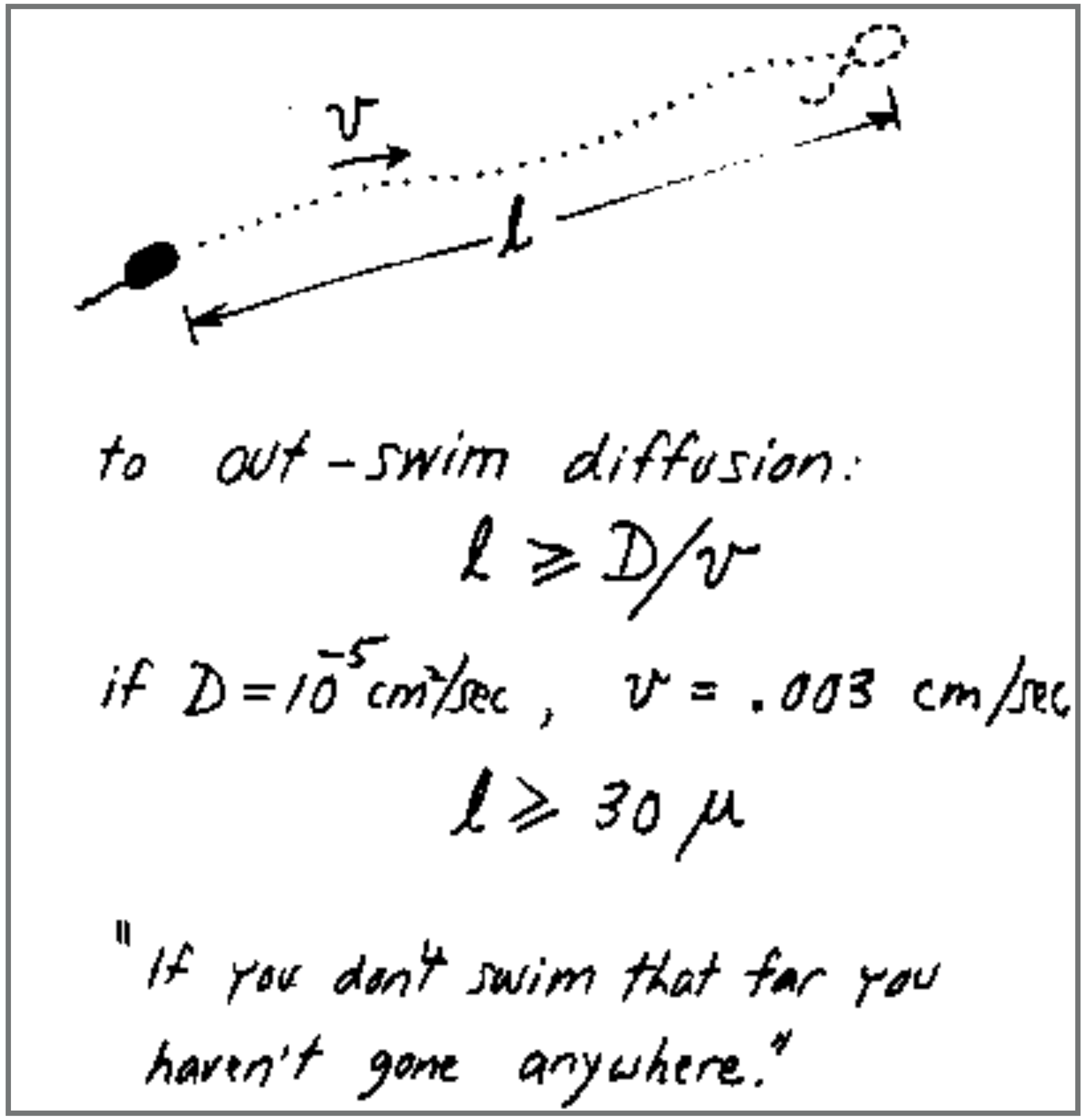
Theoretical Physics of Living Systems

Ambitious: Develop new mathematical/ principle based model of biological process. (e.g., Michaelis Menten, Hodgkin-Huxely)

Conservative: Use our understanding of physics to place limits on biological processes.

"Can **diffusion** place **limits** on how fast bacteria should swim?"

Yes! They should swim faster than 30 microns/sec to outrun diffusion.



to out-swim diffusion:

$$l \geqslant D/v$$

if $D = 10^{-5}$ cm²/sec , v = .003 cm/sec

$$l \geqslant 30\ \mu$$

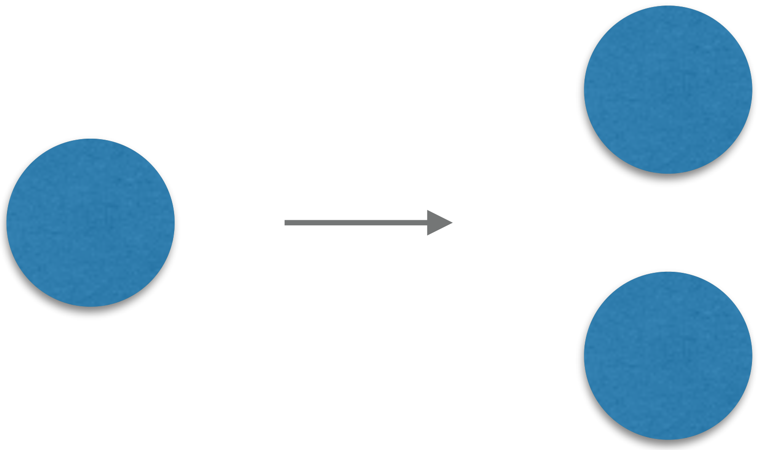
"If you don't swim that far you haven't gone anywhere."

Edward Purcell, "Life at Low Reynolds Number",1976

Self-Replication is Irreversible and Thus Produces Entropy

Self Replication

"One unit turns into two units over some period of time"



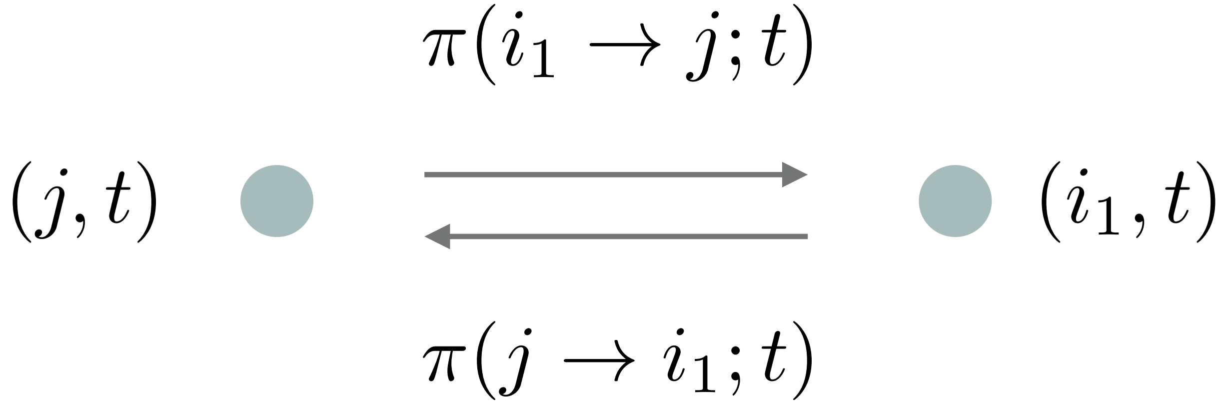
England's Argument

- Self replication is irreversible
- Irreversible processes are associated with increases in entropy

➤ Physics of entropy production (i.e., statistical physics) should place thermodynamic bounds on self replication.

Irreversibility and Entropy through Master Equation - Part 1

- Transitions to and from **a single** state

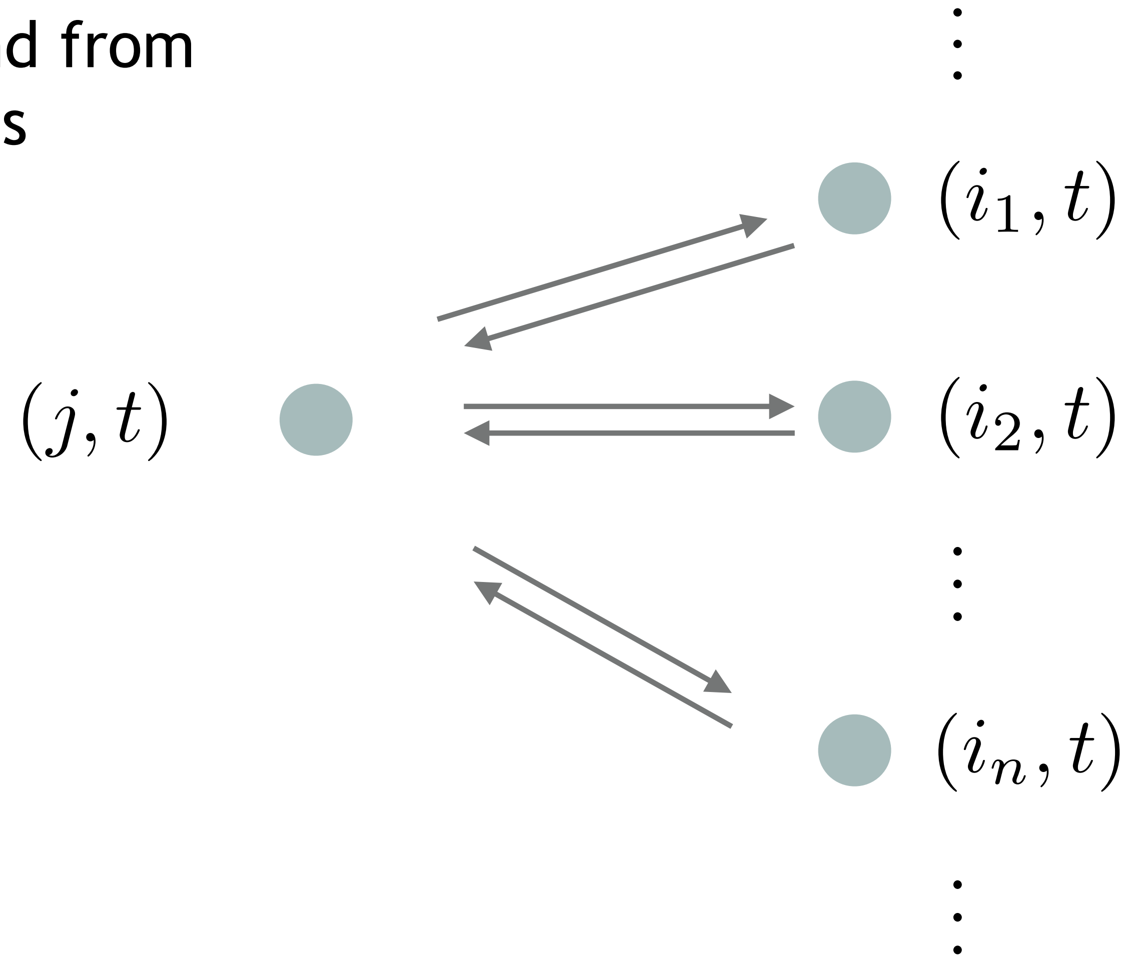


$\pi(i_1 \to j; t)$

(j, t) (i_1, t)

$\pi(j \to i_1; t)$

- Transitions to and from **all** possible states



$\vdots$

(i_1, t)

(j, t) (i_2, t)

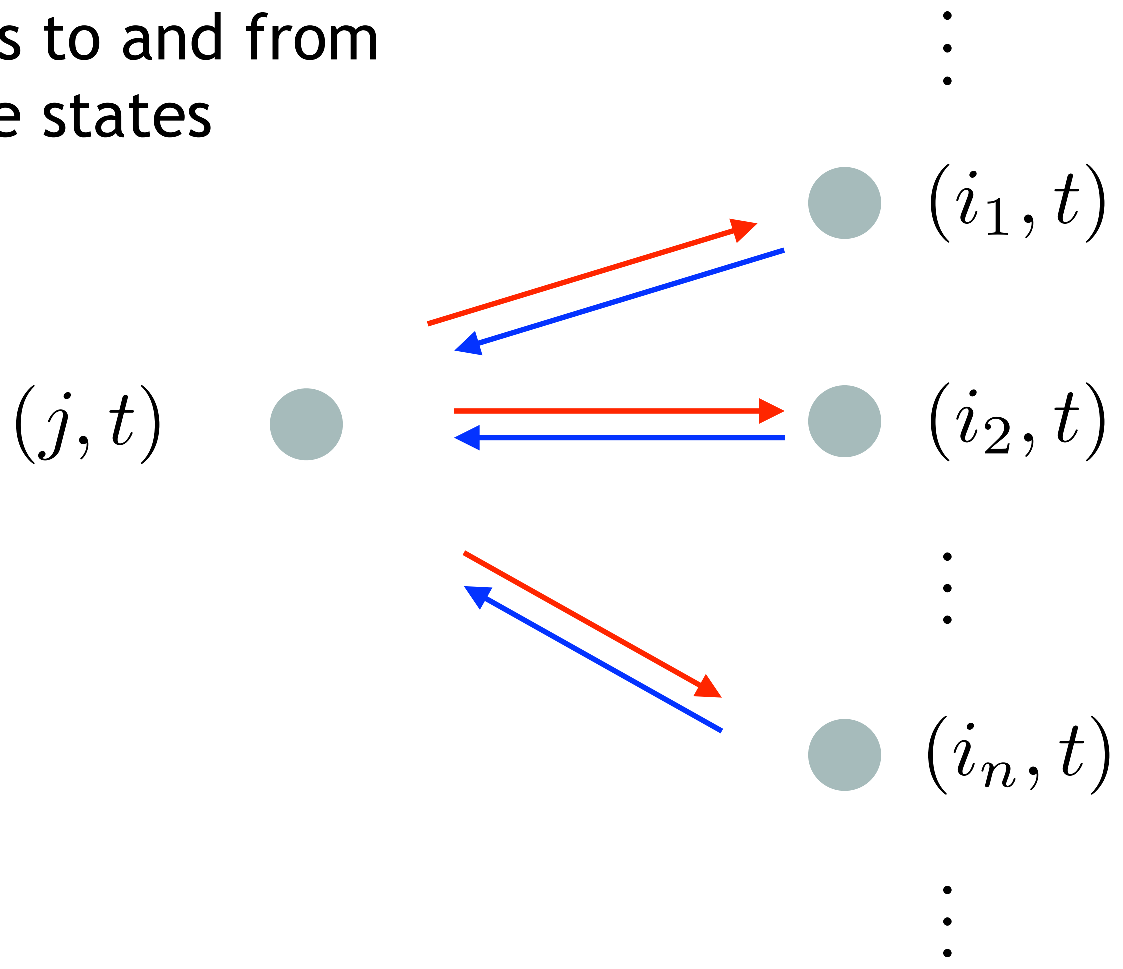
$\vdots$

(i_n, t)

$\vdots$

Irreversibility and Entropy through Master Equation - Part 2

- Transitions to and from **all** possible states



["Master Equation"]

$$\frac{\partial}{\partial t} p(j,t) = \sum_i \left[\pi(i \to j; t) p(i,t) - \pi(j \to i; t) p(j,t) \right]$$

- Foundational equation of Non-Equilibrium Statistical Physics

Irreversibility and Entropy through Master Equation - Part 3

For long times the system goes into equilibrium and is time independent

$$\lim_{t\to\infty}\Big[\pi(i\to j;t)p(i,t)-\pi(j\to i;t)p(j,t)\Big]=0$$

By thermal physics and by definition

$$\lim_{t\to\infty}p(i,t)=\frac{e^{-\beta E_i}}{Z(\beta)}$$

[“Boltzmann Distributed Energies”]

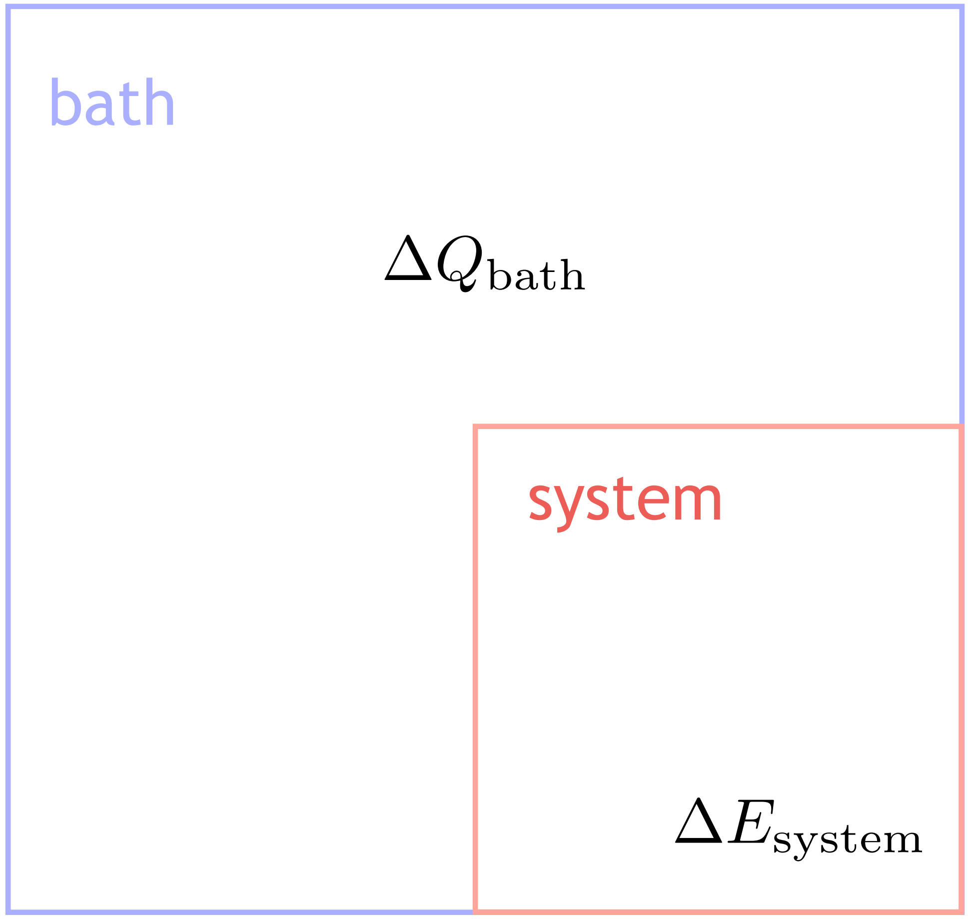
$$\lim_{t\to\infty}\pi(i\to j,t)\equiv\pi_\infty(i\to j)$$

[“Time Independent Transition Amplitude”]

Thus we have

$$\frac{\pi_\infty(j\to i)}{\pi_\infty(i\to j)}=e^{\beta\Delta E_{i\to j}}$$

Irreversibility and Entropy through Master Equation - Part 3



By conservation of Energy

$$\Delta Q_{\text{bath}} + \Delta E_{\text{system}} = \Delta E_{\text{universe}} = 0 \quad ,$$

and so we have

$$\frac{\pi_\infty(j \to i)}{\pi_\infty(i \to j)} = e^{-\beta \Delta Q_{i \to j}} \quad .$$

The definition of (dimensionless) entropy in terms of heat:

$$\Delta S = \Delta Q / k_B T$$

$$\longrightarrow \quad \boxed{\frac{\pi_\infty(j \to i)}{\pi_\infty(i \to j)} = e^{-\Delta S^{i \to j}_{\text{bath}}}}$$

- ➤ The more irreversible the reaction, the more entropy produced in the forward direction

Generalizations and Definitions

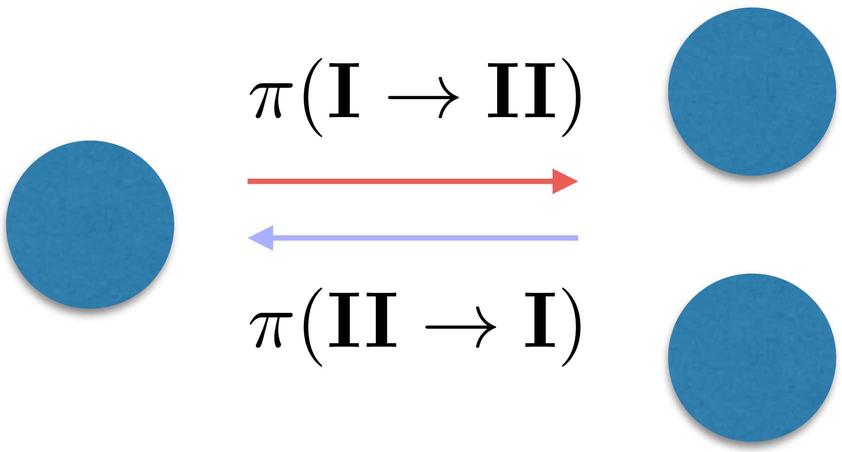
Let $i, j, k,..$ define a microstate, and $\mathbf{I}$, $\mathbf{II}$, $\mathbf{III}$, **…** define the macrostate.

Self-Replication Process

(A single unit of $\mathbf{I}$)

(Two units of $\mathbf{I}$)

Macrostate of $\mathbf{I}$, can be in any microstate *i*.



$\pi(\mathbf{I} \rightarrow \mathbf{II})$

$\pi(\mathbf{II} \rightarrow \mathbf{I})$

Macrostate of $\mathbf{II}$, can be in any microstate j.

- ➤ $\ln\left[\frac{\pi(\mathbf{II} \rightarrow \mathbf{I})}{\pi(\mathbf{I} \rightarrow \mathbf{II})}\right]$ [Defines the irreversibility of a self replication process]

Second Law of Thermodynamics — Part 1

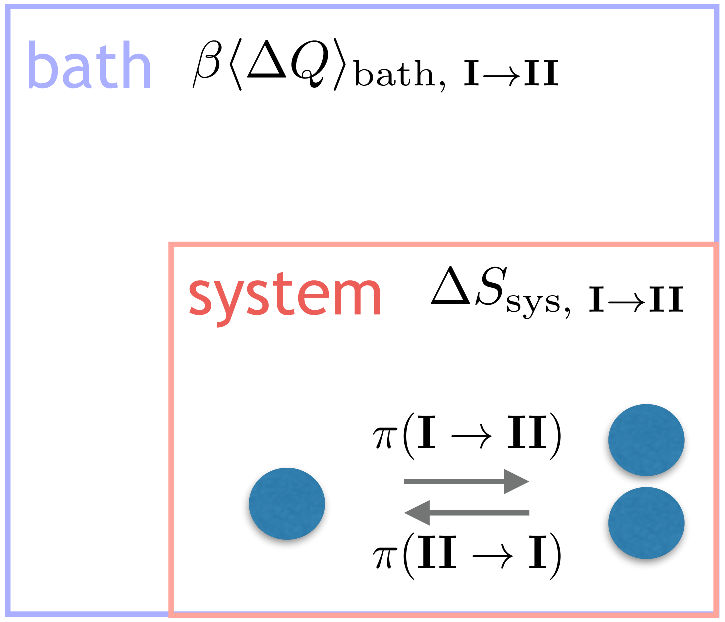
Some probability theory and algebra leads to…

Heat Released into Bath

Entropy Change of System

$$\beta\langle \Delta Q\rangle_{\text{bath, }\mathbf{I}\to\mathbf{II}} + \ln\left[\frac{\pi(\mathbf{II}\to\mathbf{I})}{\pi(\mathbf{I}\to\mathbf{II})}\right] + \Delta S_{\text{sys, }\mathbf{I}\to\mathbf{II}} \geq 0$$

Entropy Change Associated with Reaction-Irreversibility

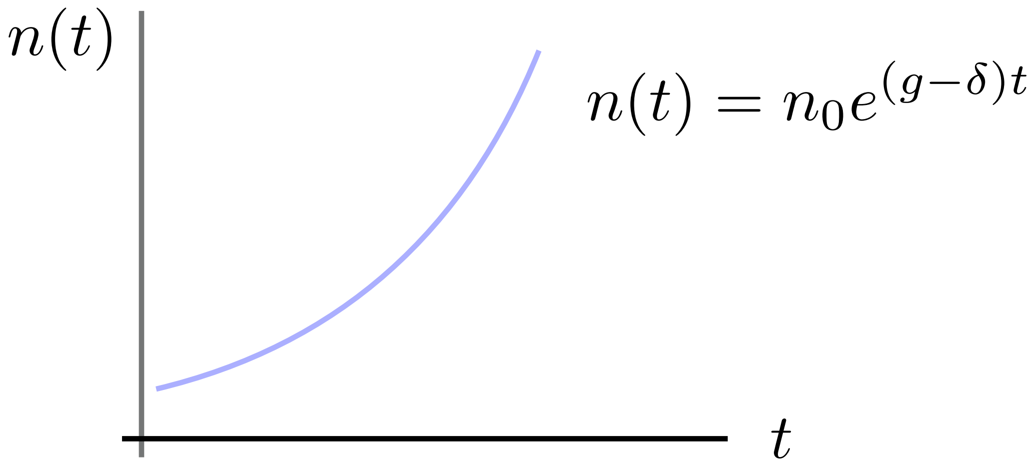


Conceptually
“Second Law of thermodynamics with macroscopic irreversibility correction”

➤ This equation applies in a wide range of far from equilibrium scenarios!

Formal to Informal Dictionary

Say we have a replicator which grows at a rate g and degrades at a rate δ



We can then define

$$\pi(\mathbf{I} \rightarrow \mathbf{II}) = g\,dt$$

[Probability of one unit to duplicate in time *dt*]

$$\pi(\mathbf{II} \rightarrow \mathbf{I}) = \delta\,dt$$

[Probability of one unit to degrade in time *dt*]

Δs_{int} [Entropy change over time *dt*]

Δq [Heat released over time *dt*]

Second Law of Thermodynamics — Part 2

$$\beta \Delta q + \Delta s_{\text{int}} \geq \ln\left[\frac{g}{\delta}\right]$$

[Main Equation of Paper]

$$\beta \Delta q + \Delta s_{\text{int}} \geq \ln\left[\frac{g}{\delta}\right]$$

Growth Rate

Degradation Rate

Heat Released

Internal Entropy Change

Two ways to look at this result:

1) <u>Maximum Ratio:</u> Given the amount of heat produced in a replication, what is the minimum ratio between growth and decay rate?

2) <u>Minimum Heat Released</u>: Given a growth rate and a decay rate, what is the minimum amount of heat released during replication/growth?

Maximum Net-Growth Rate (i.e., Fitness)

We can also compute

Net Growth Rate

Degradation Rate

$$g_{\max} - \delta = \delta\left(\exp[\beta \Delta q + \Delta s_{\text{int}}] - 1\right)$$

Maximum Fitness

Heat Released

Internal Entropy Change

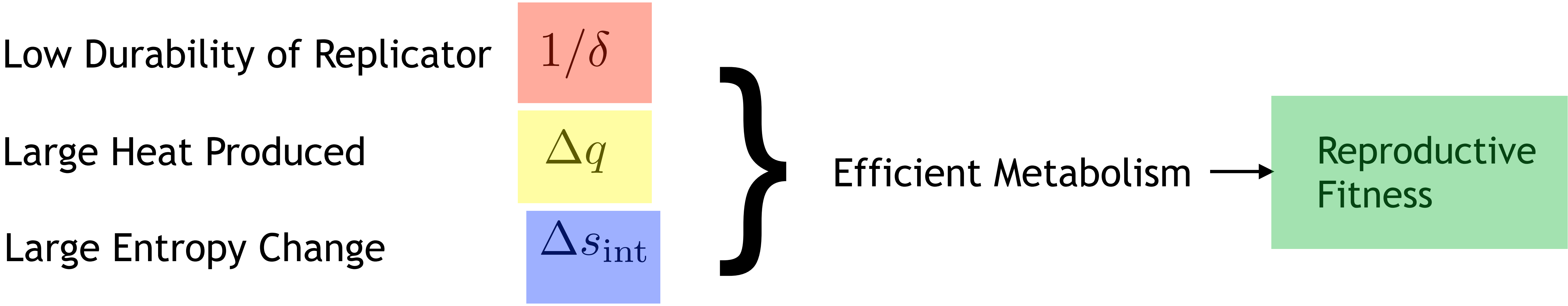
> "Replicator's maximum potential fitness is set by how it exploits energy in its environment to catalyze it's own reproduction."

Reproductive Fitness depends on Efficient Metabolism

Application: Bacterial Cell Division

Main Qualitative Prediction of Work

$$g_{\text{max}} - \delta = \delta\left(\exp[\beta\Delta q + \Delta s_{\text{int}}] - 1\right)$$



Low Durability of Replicator $1/\delta$

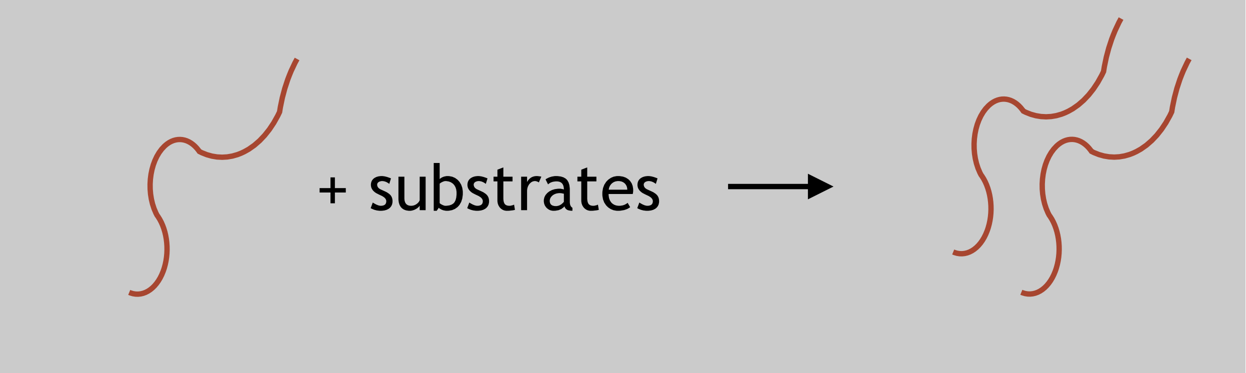
Large Heat Produced Δq

Large Entropy Change Δs_{int}

$\}$ Efficient Metabolism → Reproductive Fitness

Application: Self-Replicating Polynucleotides

Self Replicating RNA Enzyme:



Doubling Time: 1 hour

Lincoln, Tracey A., and Gerald F. Joyce, *Science (2009)*

Cleavage Rate (i.e. Half Life): 4 years

Thompson, James E., et al. *Bioorganic chemistry (1995)*

$$\ln\left[\frac{g}{\delta}\right] = \ln\left[\frac{4\text{ years}}{1\text{ hr}}\right]$$

* Change in Internal Entropy: Negligible (Mixing Entropy of Reactants ~ Mixing Entropy of Products)

➤ $\langle \Delta Q \rangle \geq RT \ln(g/\delta) = 7\ \mathrm{kcal/mol}$

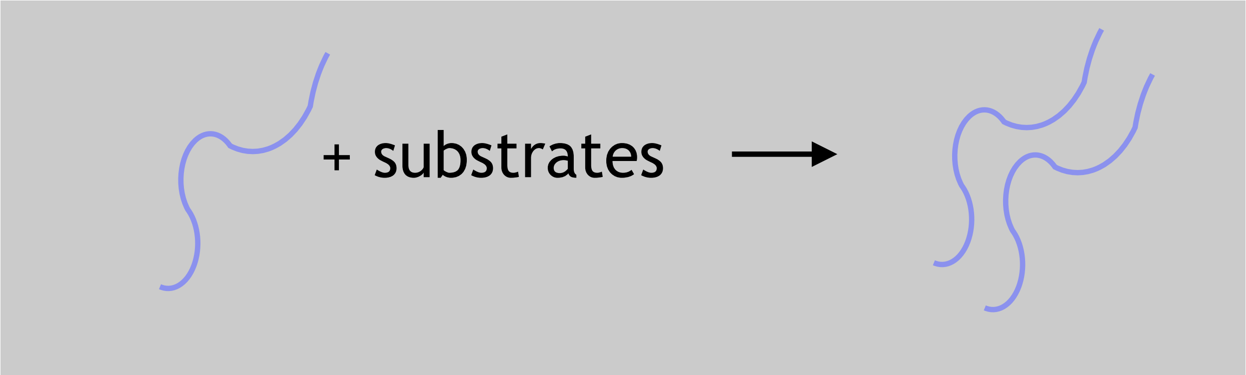
Experimentally, the heat released is 10 kcal/mol →

Minetti, Conceição ASA, et al. "Proceedings of the National Academy of Sciences (2003)

Replicating RNA enzyme operates close to thermodynamic efficiency

Application: Self-Replicating Polynucleotides

(Hypothetical!) Self Replicating **Single Stranded DNA**:



Doubling Time: 1 hour

Cleavage Rate (i.e. Half Life): 3 X 10^7 years

$$\ln\left[\frac{g}{\delta}\right] = \ln\left[\frac{4 \text{ years}}{1 \text{ hr}}\right]$$

Schroeder, Gottfried K., *et al. PNAS of the United States of America 103.11 (2006)*

- $\langle \Delta Q \rangle \geq RT \ln(g/\delta) = 16 \text{ kcal/mol} > \text{ enthalpy of ligation reaction}$

DNA self-replication (of this kind) is forbidden thermodynamically! →

Does this relate to why RNA (and not DNA) was the self-replicating nucleic acid on prebiotic earth?