Aging and Failure in Biological, Physical and Material Systems

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Overview of first-passage phenomena

Telomere dynamics & immortality transition

perhaps of dubious significance but not wrong

How long is a hospitalization?

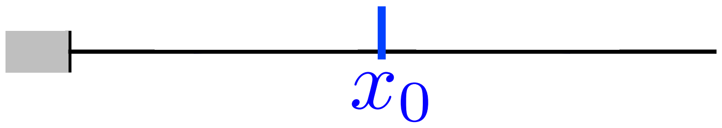
a tentative attempt to describe failure

First-Passage Probability in 1d

A Guide to First-Passage Processes, SR (Cambridge, 2001)

When does a random walk ***first*** hit the origin?

$$\begin{cases} \frac{\partial P(x,t)}{\partial t} = D\frac{\partial^2 P(x,t)}{\partial x^2} \\ P(x,0) = \delta(x-x_0) \\ P(0,t) = 0 \end{cases}$$



solve for the first-passage probability

First-Passage Probability in 1d

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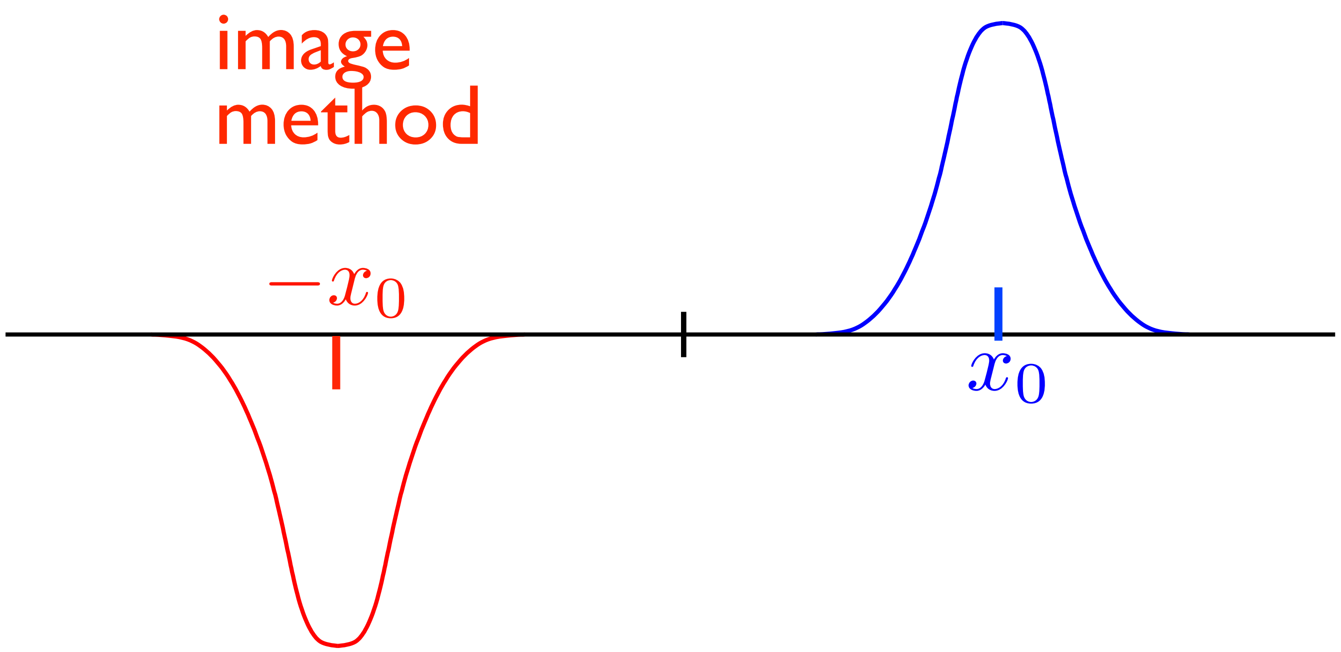
When does a random walk ***first*** hit the origin?



$$c(x,t) = \frac{1}{\sqrt{4\pi Dt}}\left[-e^{-(x+x_0)^2/4Dt} + e^{-(x-x_0)^2/4Dt}\right]$$

first-passage probability:

$$F(x_0,t) = D\frac{\partial c}{\partial x}\Big|_{x=0} = \frac{x_0}{\sqrt{4\pi Dt^3}}\, e^{-x_0^2/4Dt}$$

First-Passage Probability in 1d

$$F(x_0,t) = D\frac{\partial c}{\partial x}\Big|_{x=0} = \frac{x_0}{\sqrt{4Dt^3}}\, e^{-x_0^2/4Dt}$$

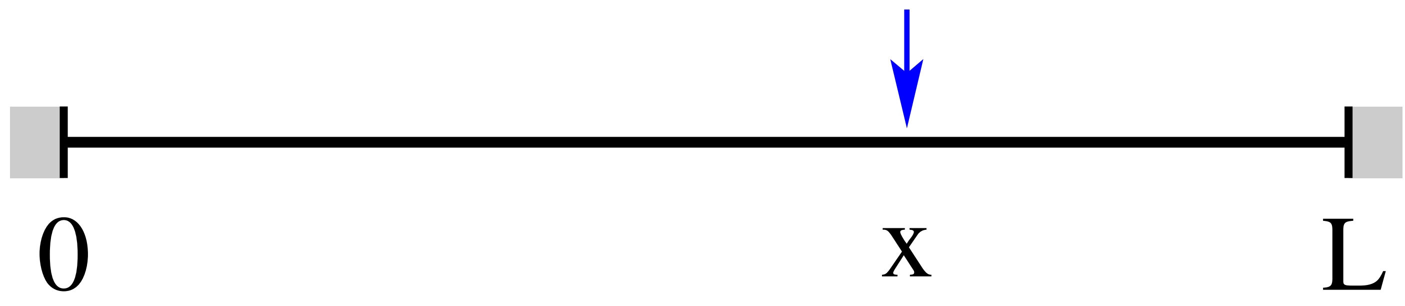
three basic facts:

1. $\displaystyle\int_0^\infty F(x_0,t)\,dt = 1$ *hitting is certain*

2. $\displaystyle\langle t\rangle \equiv \int_0^\infty t\,F(x_0,t)\,dt = \infty$ *infinite lifetime*

3. $\displaystyle S(t) = 1 - \int_0^t F(x_0,t')\,dt'$
$\displaystyle = \mathrm{erf}\left(\frac{x_0}{\sqrt{4Dt}}\right) \simeq \frac{x_0}{\sqrt{4Dt}}$ *slowly decaying survival probability*

First Passage in the Interval



- *Survival probability?* $S(t) \sim e^{-t/L^2}$
- *Splitting probability* to 0 & L? $p_{\rm left} = \frac{x}{L}$ $p_{\rm right} = 1 - \frac{x}{L}$
- *First-passage probability* to 0 & L? infinite series
- *Exit time?* $t(x) = \frac{x(L-x)}{2D}$
- *Conditional exit time* to 0 & L?

$$t_{\rm left}(x) = \frac{x(2L-x)}{6D}$$

$$t_{\rm right}(x) = \frac{L^2 - x^2}{6D}$$

First Passage in the Interval

Splitting probability to 0 & L

by time-integrated or backward Kolmogorov equation

$$\mathcal{E}(x) = \sum_{\text{paths}} \Pi_{x \to L}$$

First Passage in the Interval

Splitting probability to 0 & L

by time-integrated or backward Kolmogorov equation

$$\mathcal{E}(x) = \sum_{\text{paths}} \Pi_{x\to L} = \frac{1}{2}\sum_{\text{paths}'} \Pi_{x+dx\to L} + \frac{1}{2}\sum_{\text{paths}''} \Pi_{x-dx\to L}$$

First Passage in the Interval

Splitting probability to 0 & L

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$$\mathcal{E}(x) = \sum_{\text{paths}} \Pi_{x\to L} = \frac{1}{2}\sum_{\text{paths}'} \Pi_{x+dx\to L} + \frac{1}{2}\sum_{\text{paths}''} \Pi_{x-dx\to L}$$

$$= \frac{1}{2}\mathcal{E}(x+dx) \qquad + \frac{1}{2}\mathcal{E}(x-dx)$$

$$\to \mathcal{E}'' = 0 \qquad \mathcal{E}(0) = 0 \quad \mathcal{E}(L) = 1$$

Laplace Equation

$$\to \mathcal{E}(x) = \frac{x}{L}$$

First Passage in the Interval

Average unconditional exit time

by time-integrated or backward Kolmogorov equation

$$t(x) = \sum_{\text{paths}} (\Pi\, t)_{x\to\pm L} = \tfrac{1}{2}\sum_{\text{paths}}\left\{\Pi'\,[dt + t_{x+dx\to\pm L}]\right\} + \tfrac{1}{2}\sum_{\text{paths}}\left\{\Pi''\,[dt + t_{x-dx\to\pm L}]\right\}$$

$$= dt \quad + \tfrac{1}{2}\, t(x+dx) \qquad\qquad + \tfrac{1}{2}\, t(x-dx)$$

$$\to 0 = dt + \tfrac{1}{2}(dx)^2\, t''(x) \qquad \to Dt'' = -1 \qquad D = \frac{(dx)^2}{2\,dt}$$

$$t(0) = t(L) = 0$$

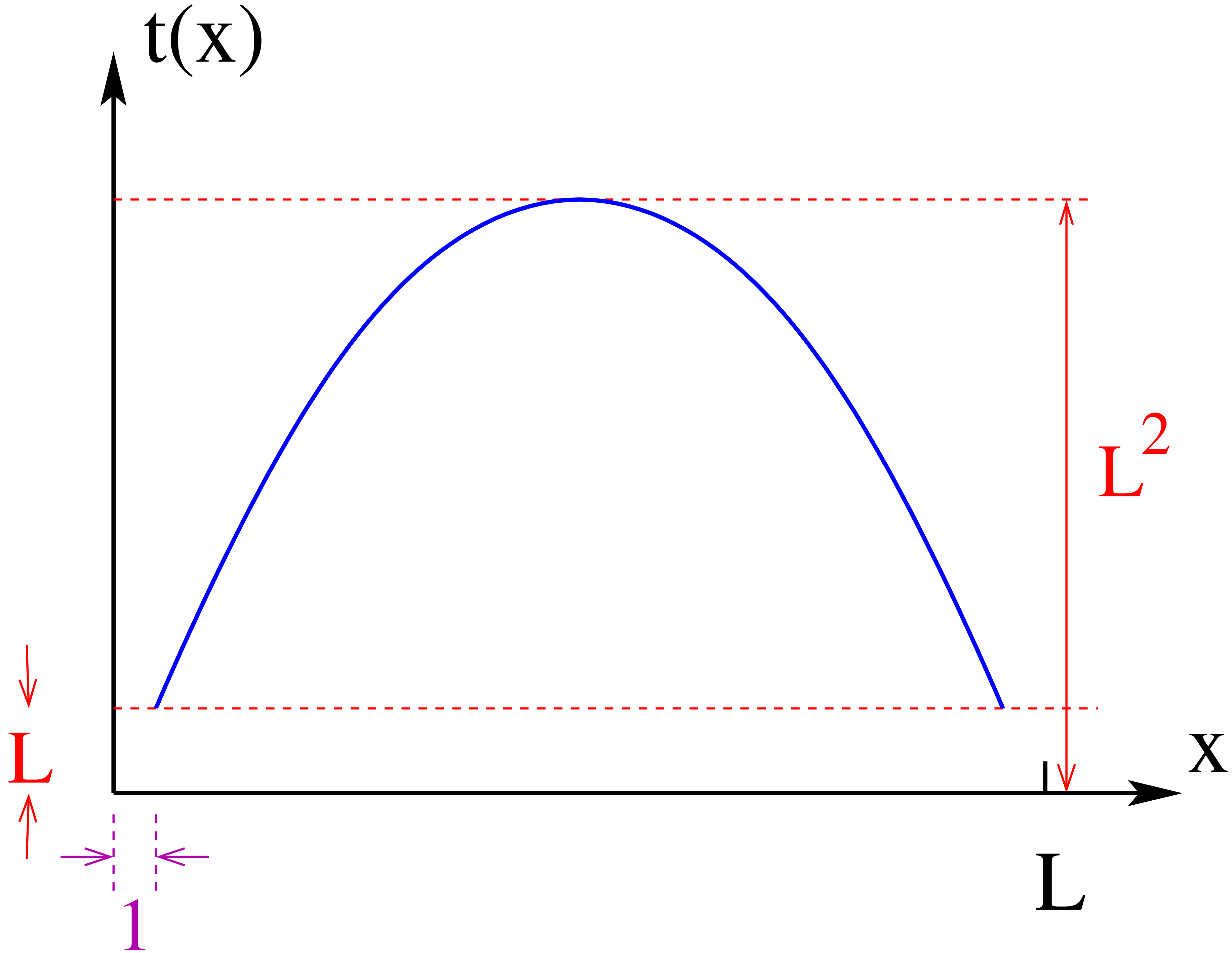
$$t(x) = \frac{x(L-x)}{2D}$$

Poisson Equation

First Passage in the Interval

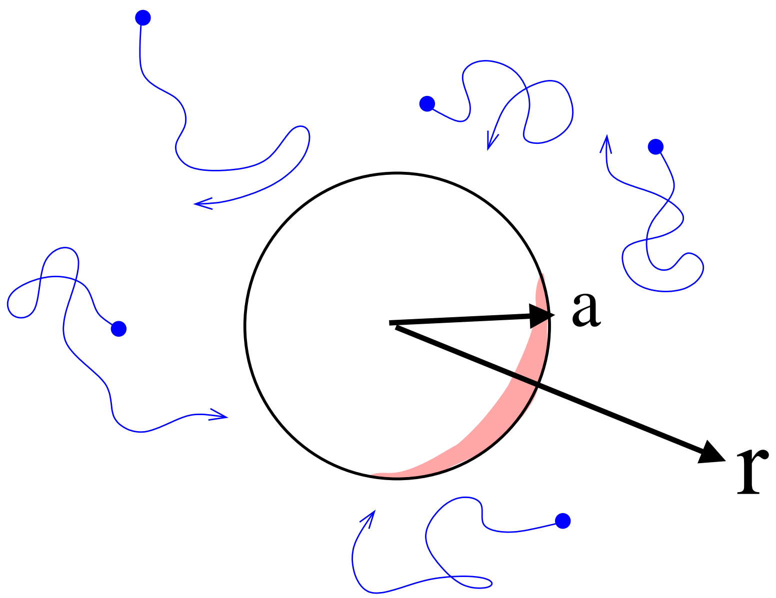
Average unconditional exit time

$$t(x) = \frac{x(L-x)}{2D}$$



First-Passage in Spherical Geometry

What is the eventual hitting probability $\mathcal{E}(r)$?



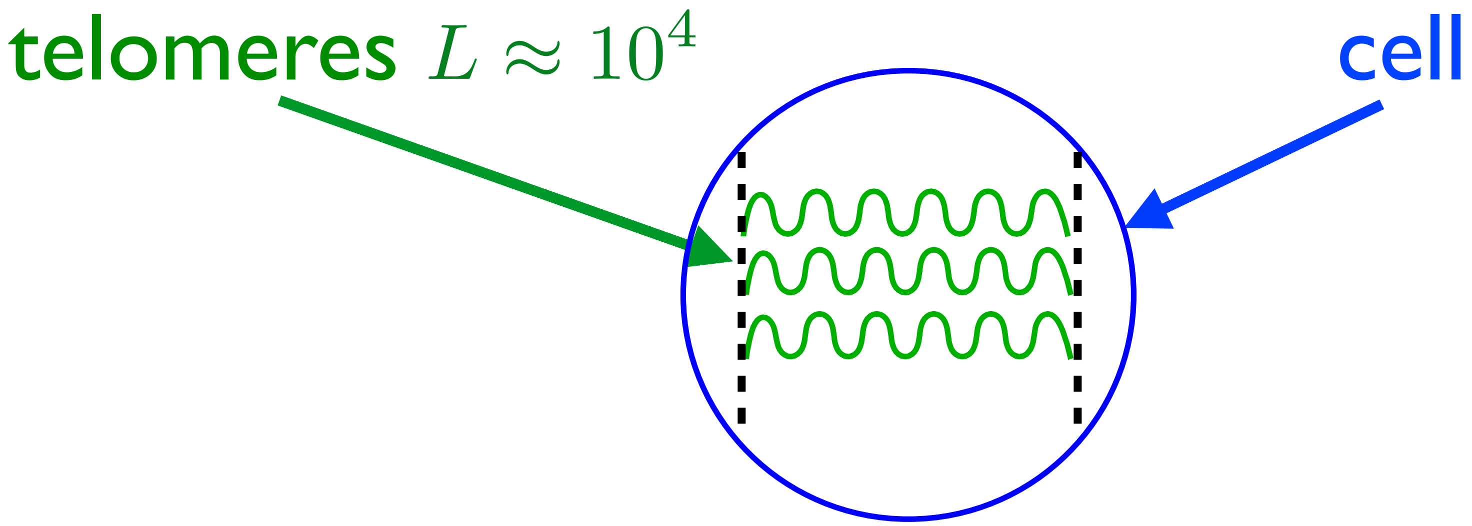
Solve:

$$\begin{cases} \nabla^2 \mathcal{E}(r) = 0 \\ \mathcal{E}(a) = 1, \ \mathcal{E}(\infty) = 0 \end{cases}$$

$$\mathcal{E}(r) = \frac{a}{r}$$

Cell Senescence Statistics

Antal, Blagoev, Trugman, SR, JTB 2007



$$\Delta L_{\mathrm{det}} \approx -10^2 \qquad \Delta L_{\mathrm{sto}} \approx \pm 10^2$$

Model

Model

biased

deterministic
telomere
shortening

Model

biased

branching

deterministic
telomere
shortening

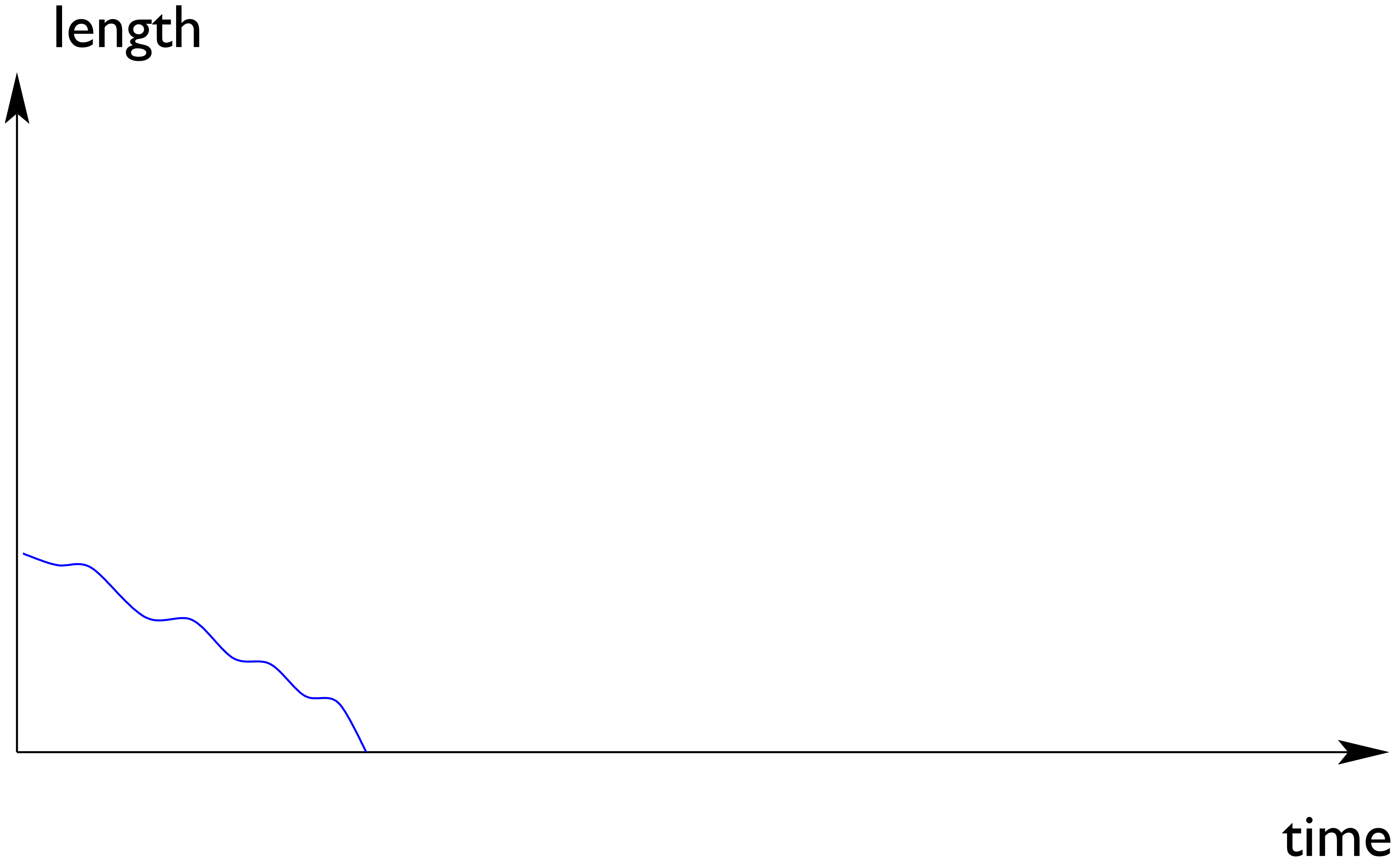
cell
division

Model

Kesten (1978)

biased	*branching*	*random walk*
deterministic telomere shortening	cell division	stochastic exchange

Schematic Evolution
(1 telomere/cell)



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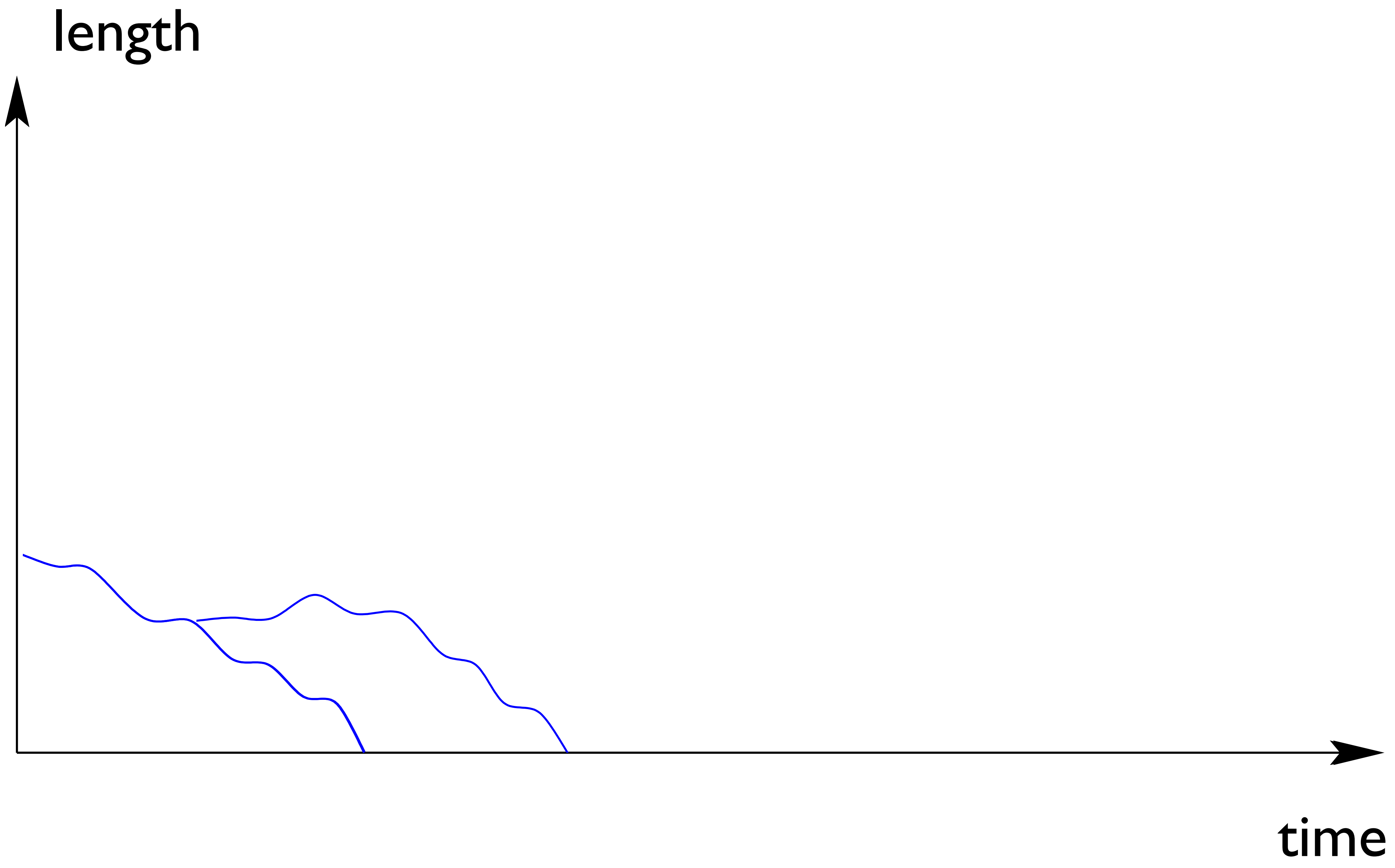

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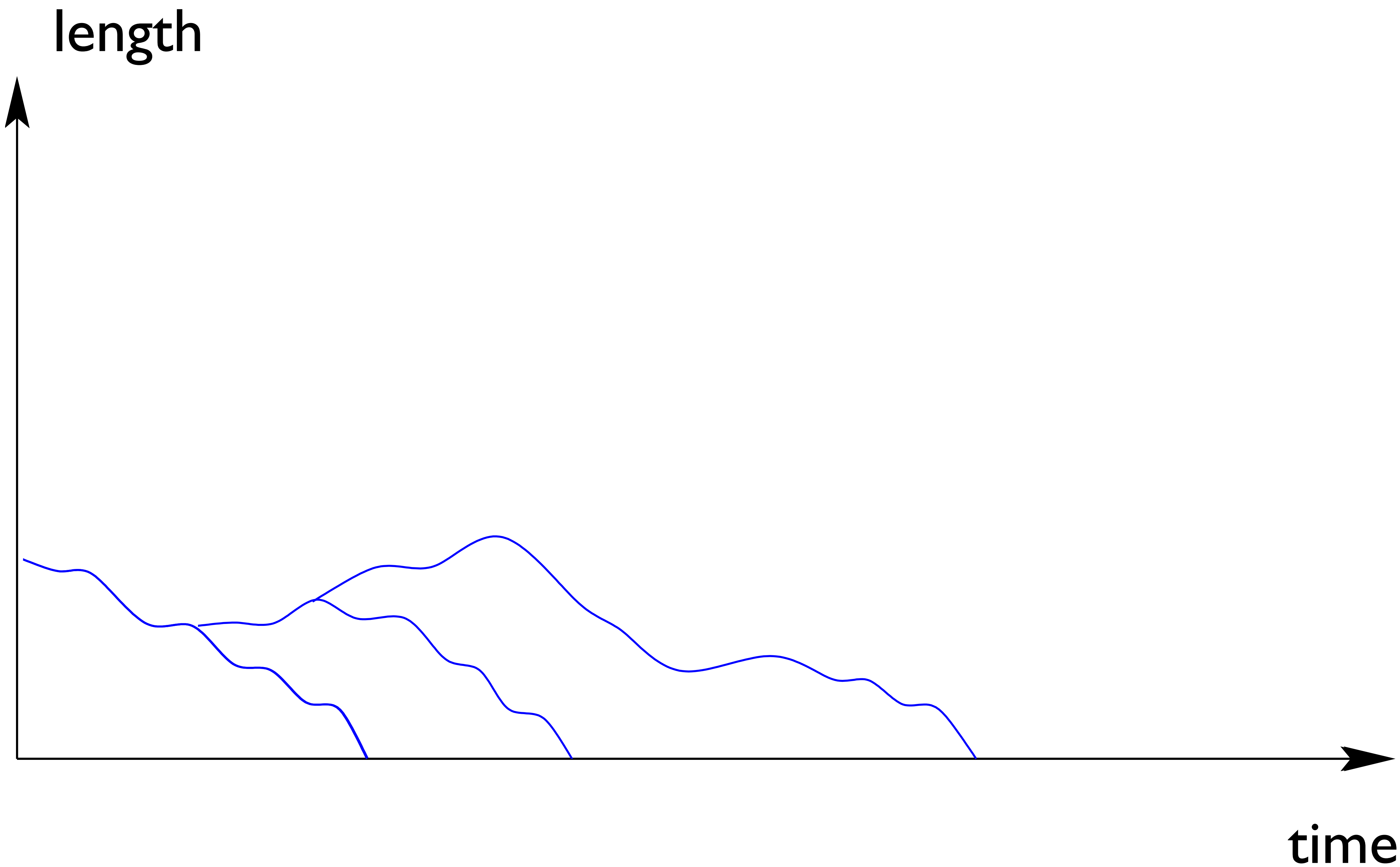

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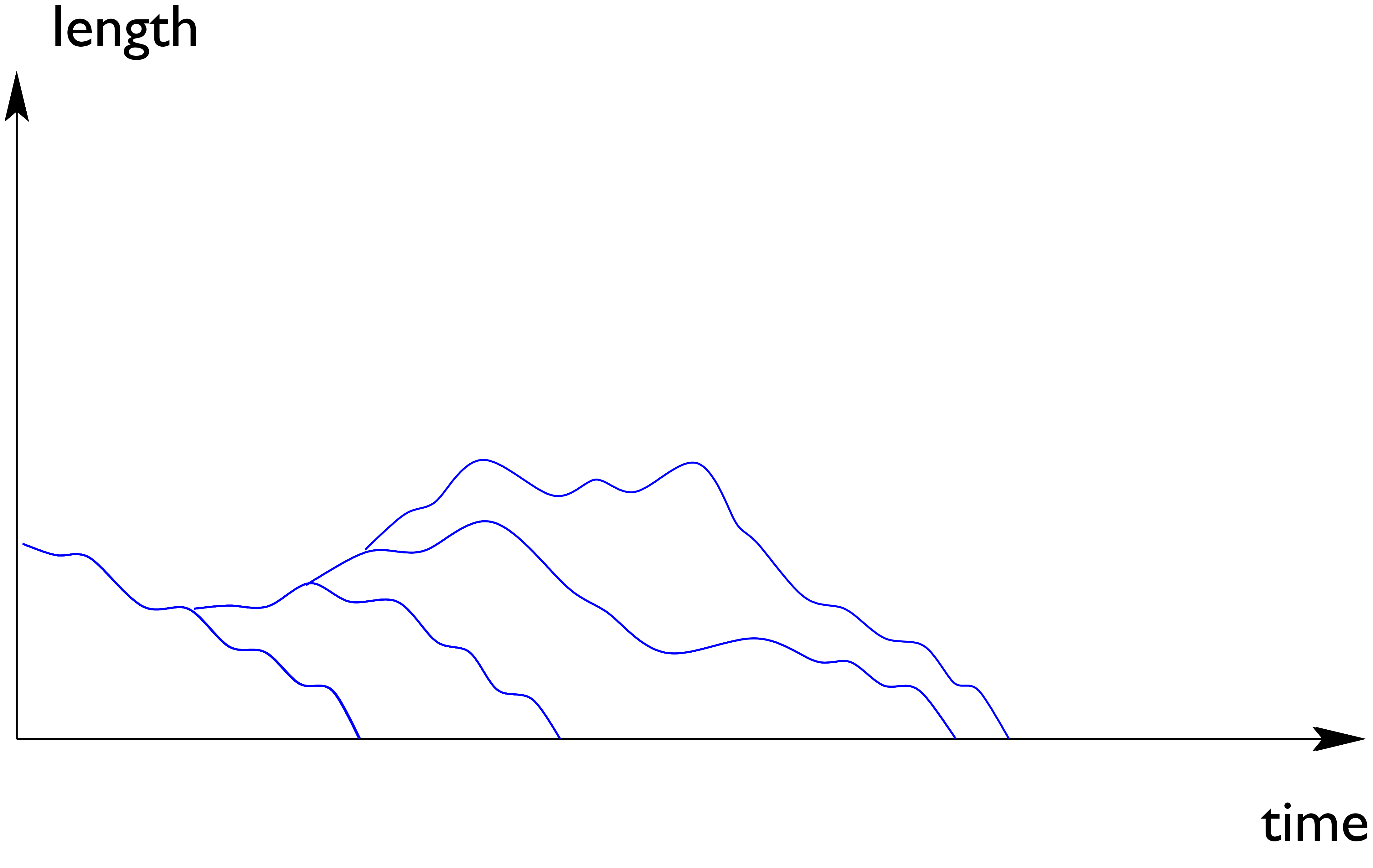

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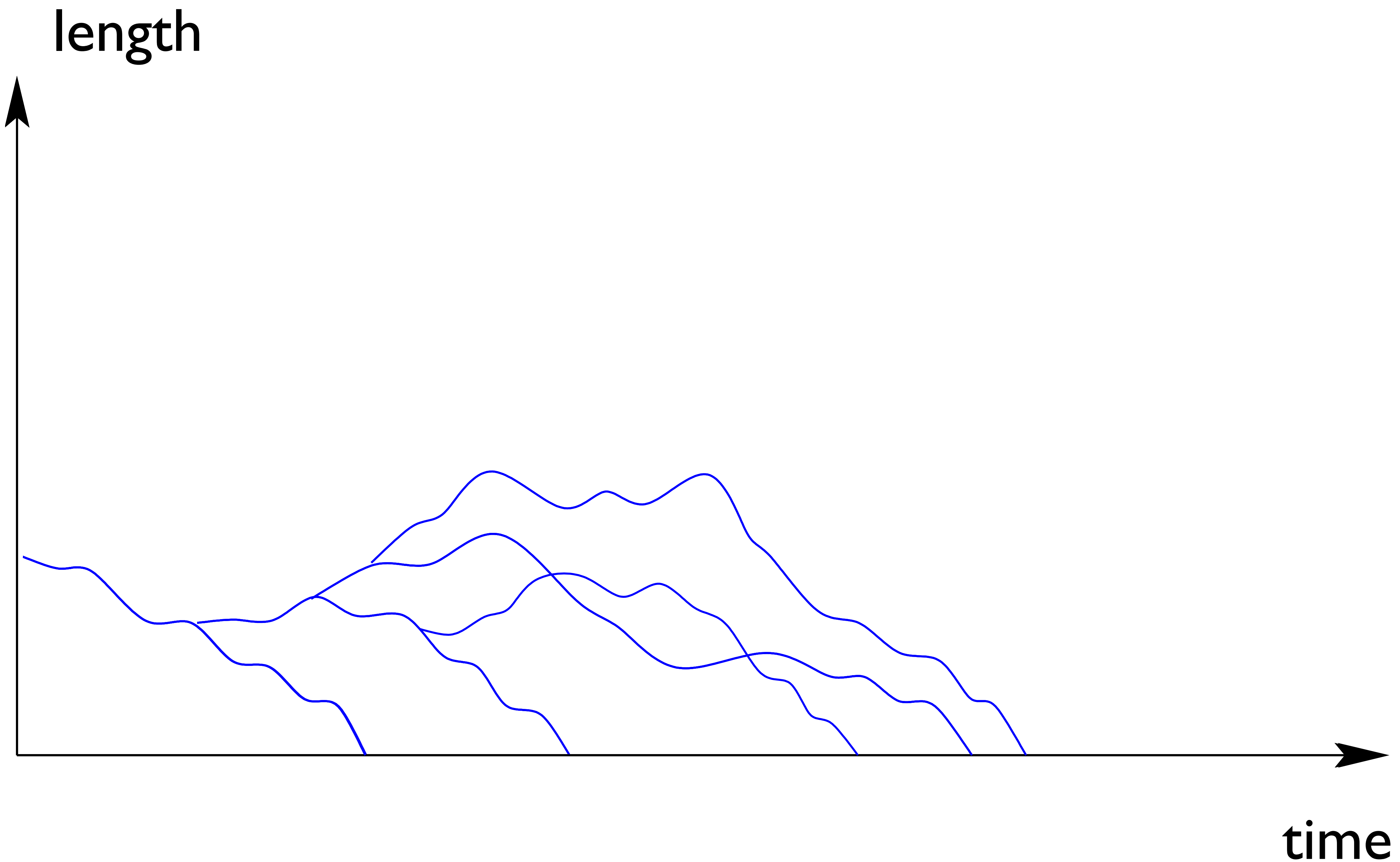

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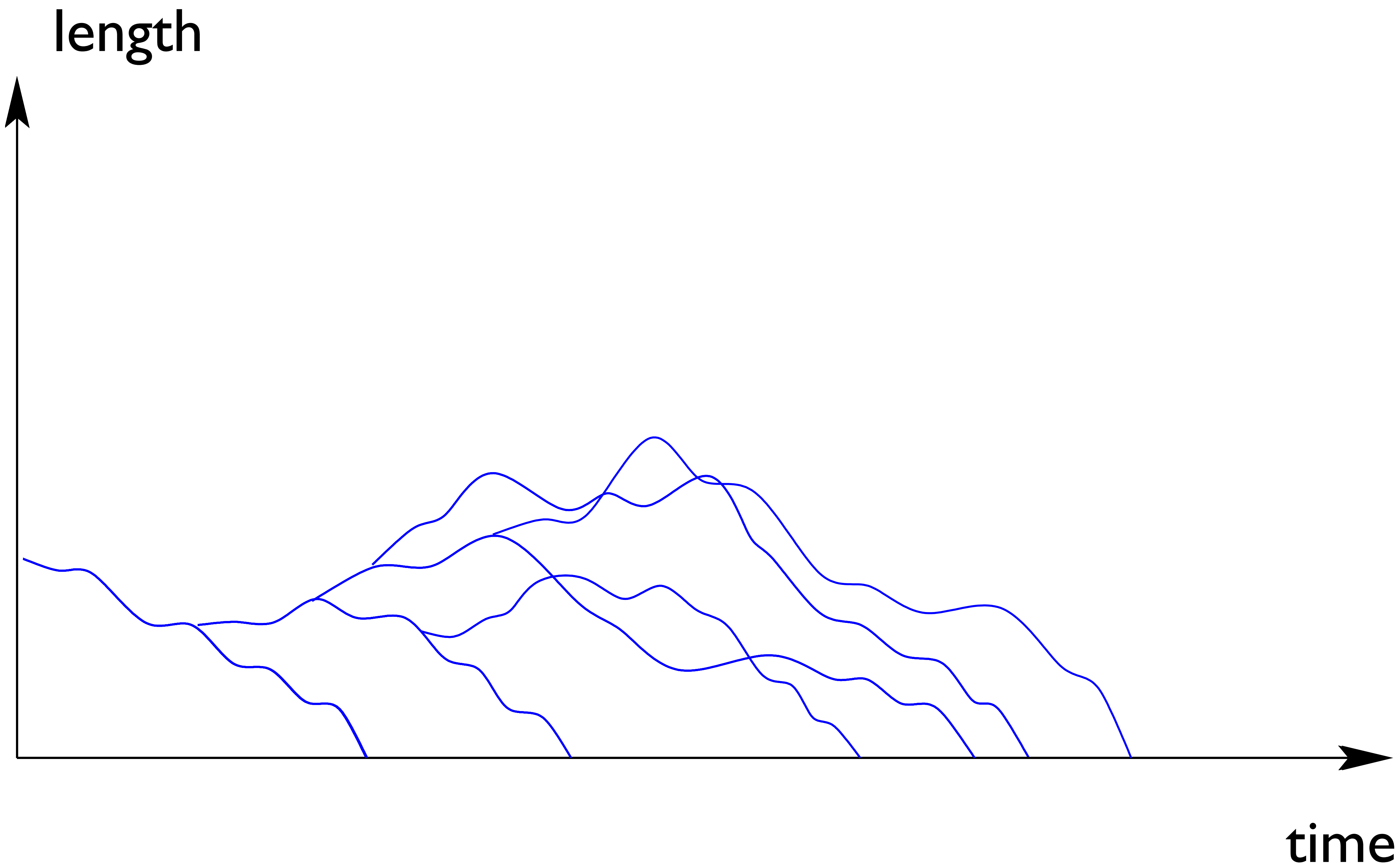

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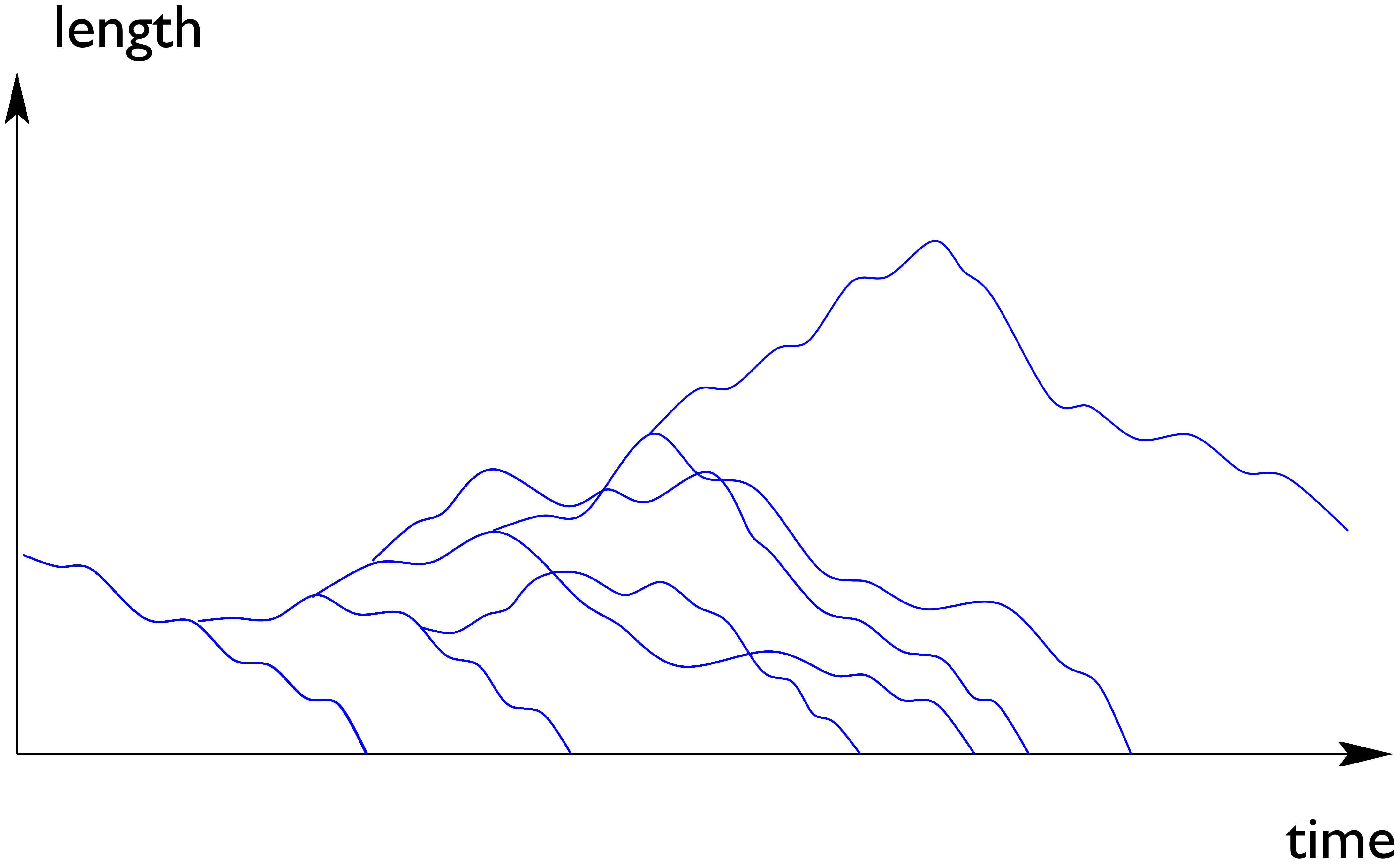

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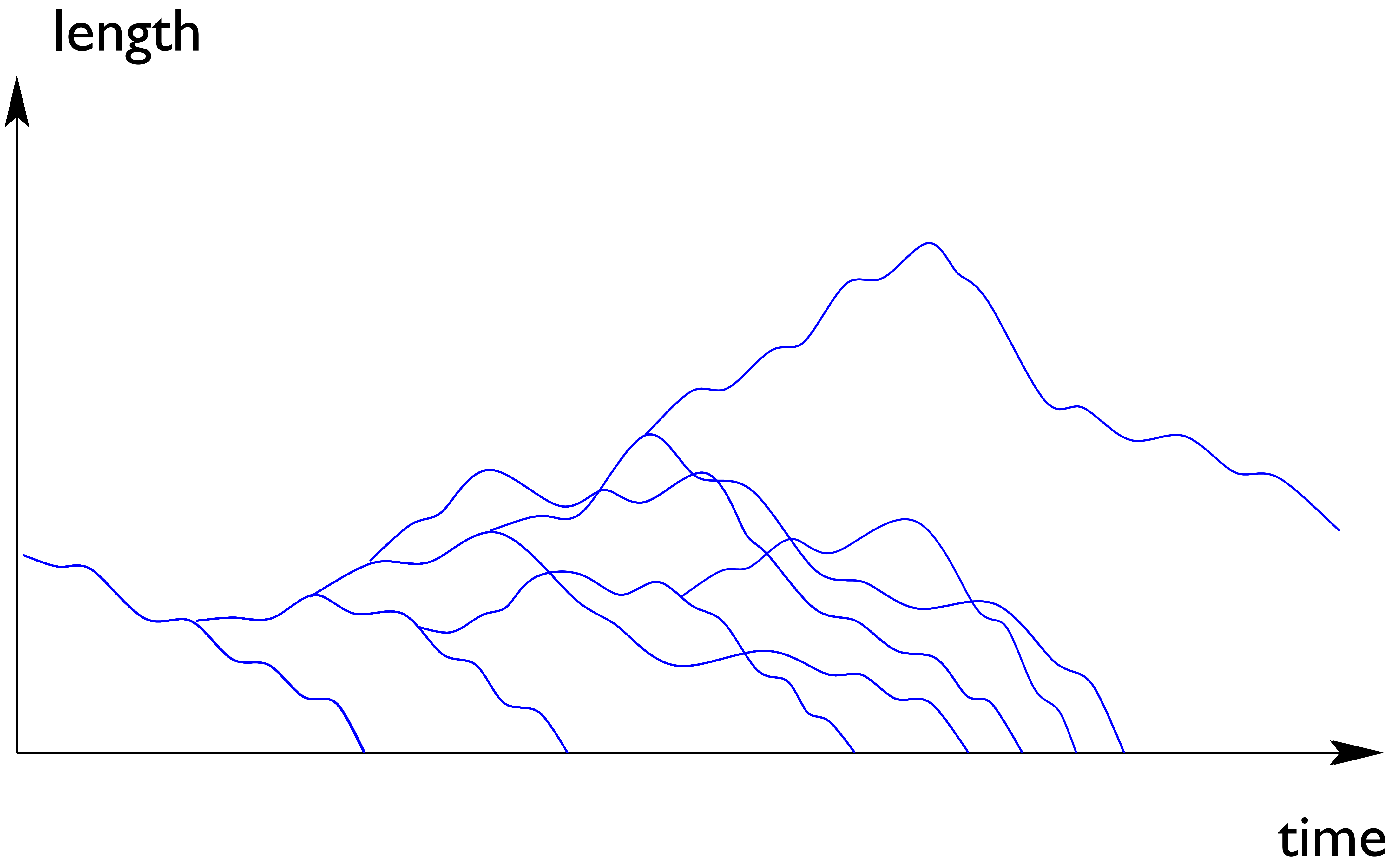

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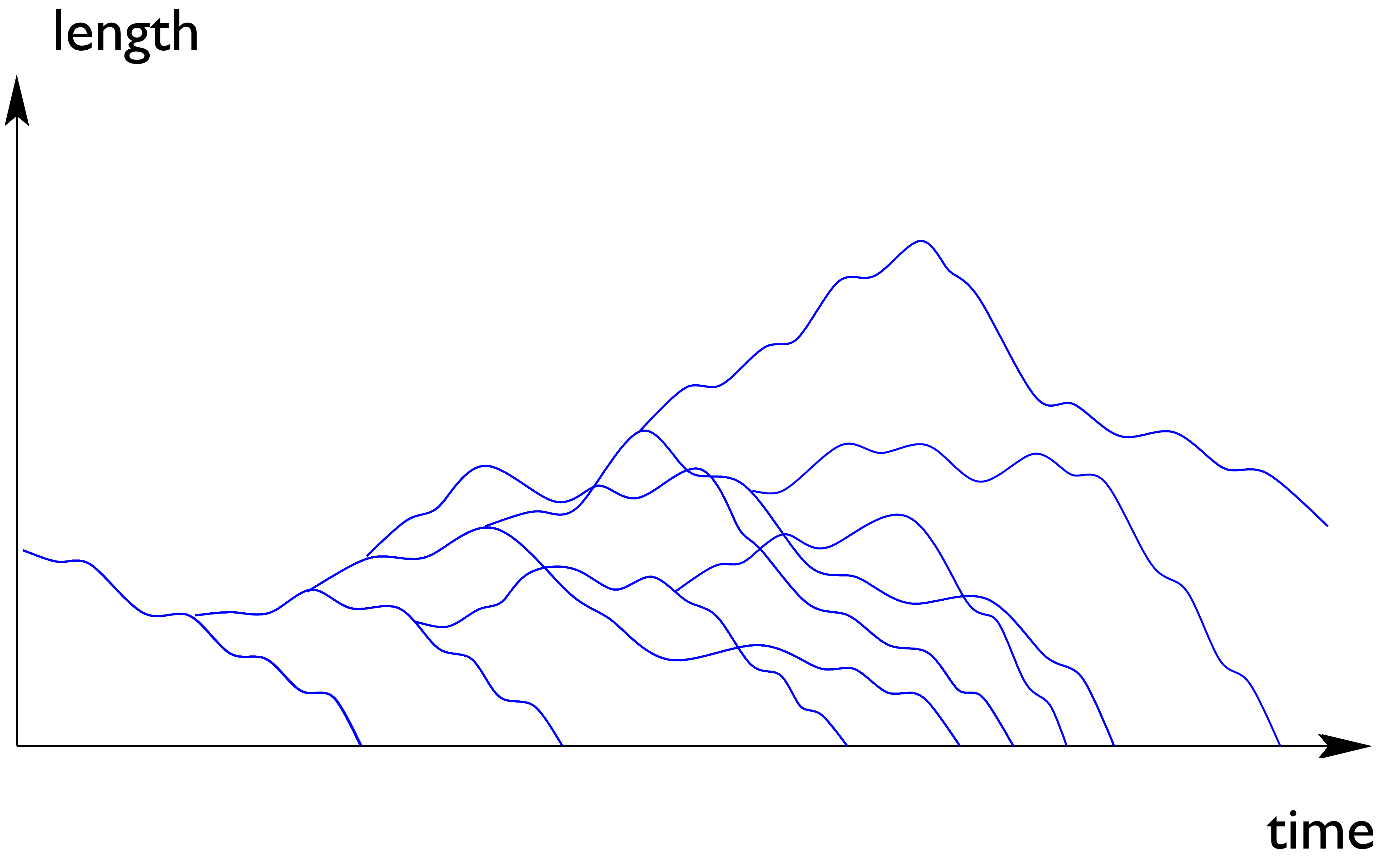

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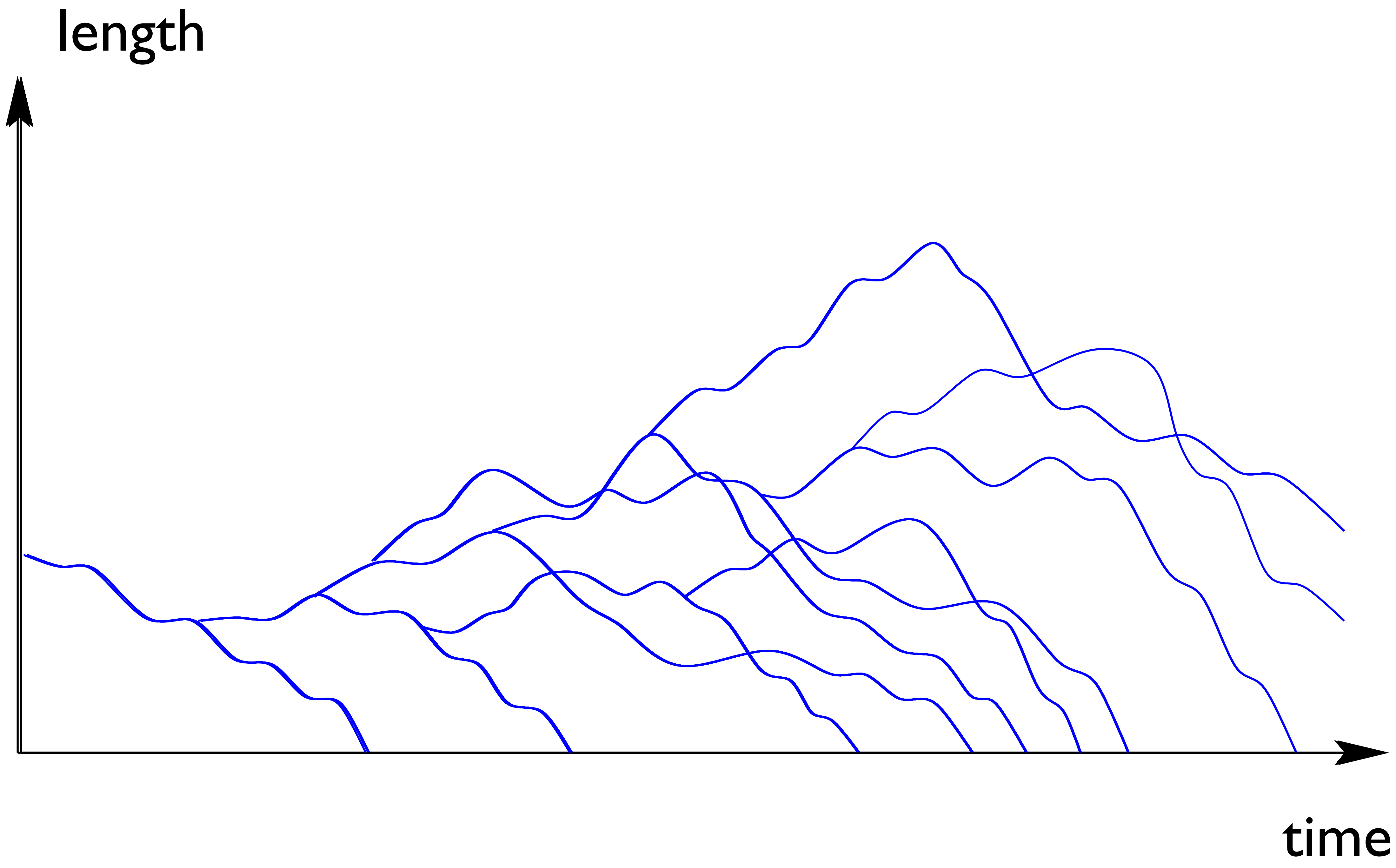

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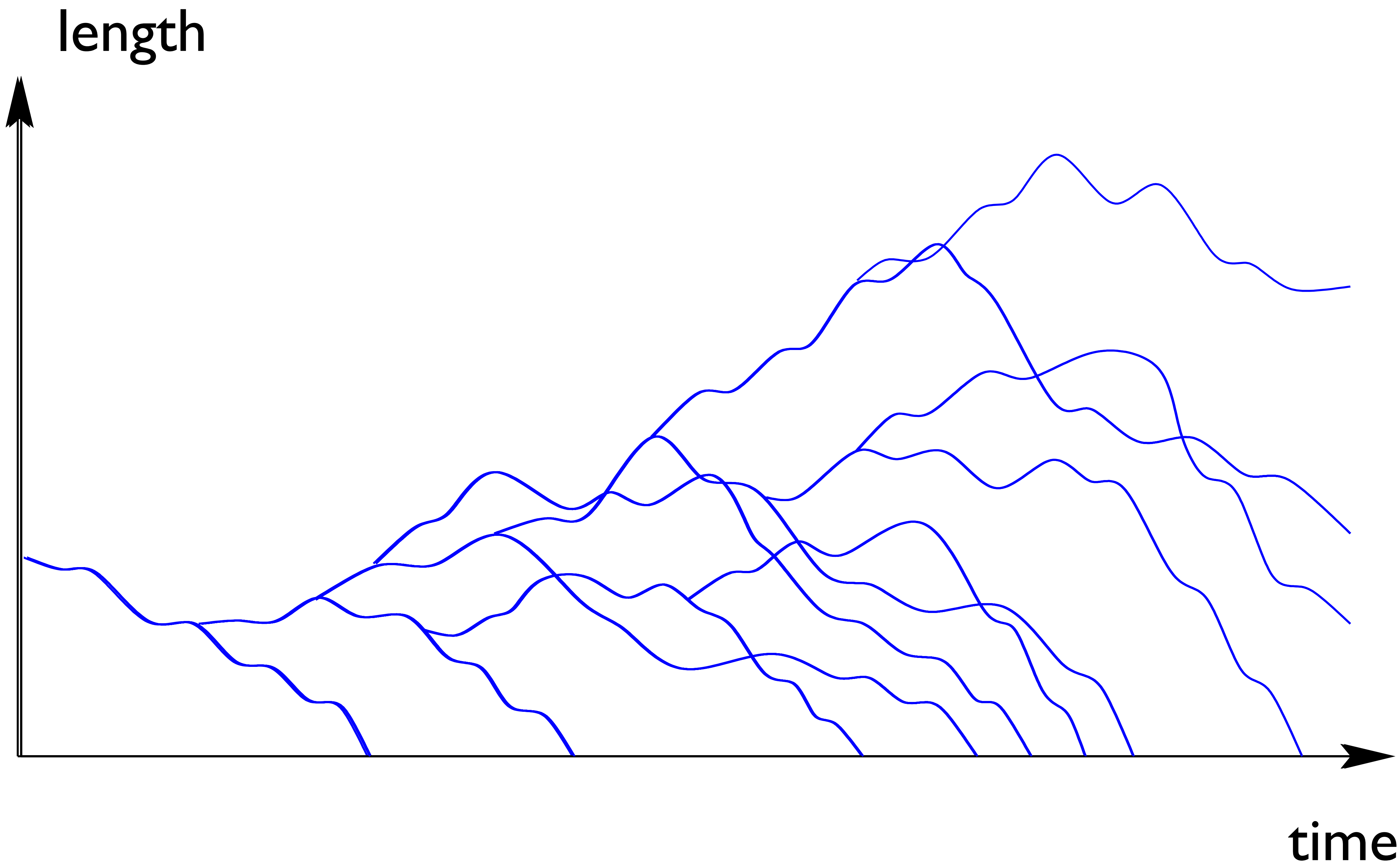

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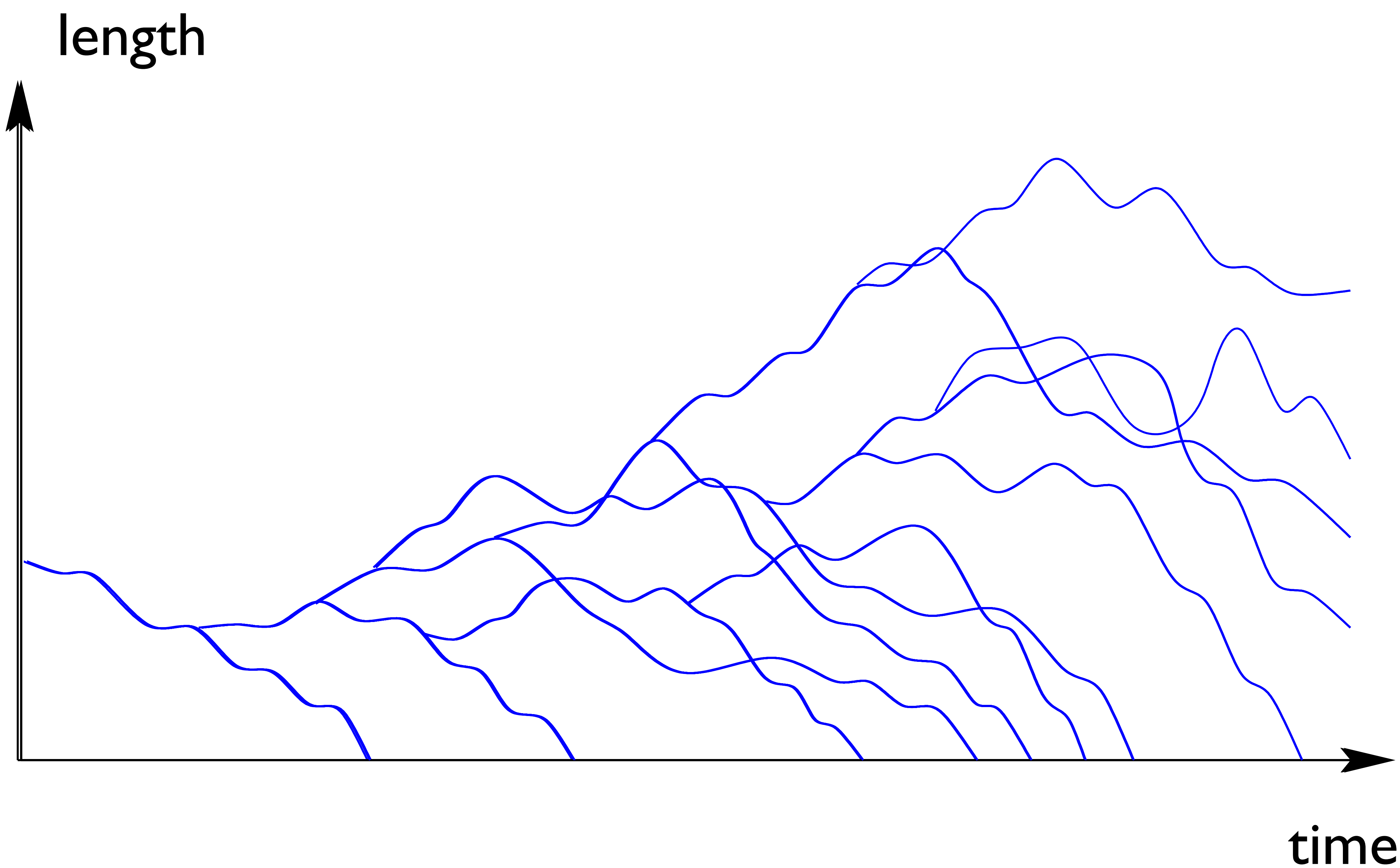


Number of Cells & Lifetime
(1 telomere/cell)

number of cells with telomere of length x at time t

$$c(x,t) = \frac{e^{kt}}{\sqrt{4\pi D t}}\left[e^{-(x-x_0-vt)^2/4Dt} - e^{-vx_0/D}e^{-(x+x_0-vt)^2/4Dt}\right]$$

number of living cells at time t

$$N(t) = \int_0^\infty c(x,t)\,dx \simeq \sqrt{\frac{4Dt}{\pi}}\frac{x_0}{(vt)^2}\; e^{-vx_0/2D}\; e^{kt(1-v^2/4Dk)}$$

average cell lifetime

$$\langle t\rangle = \frac{x_0}{v}\frac{1}{\sqrt{1-4Dk/v^2}}$$

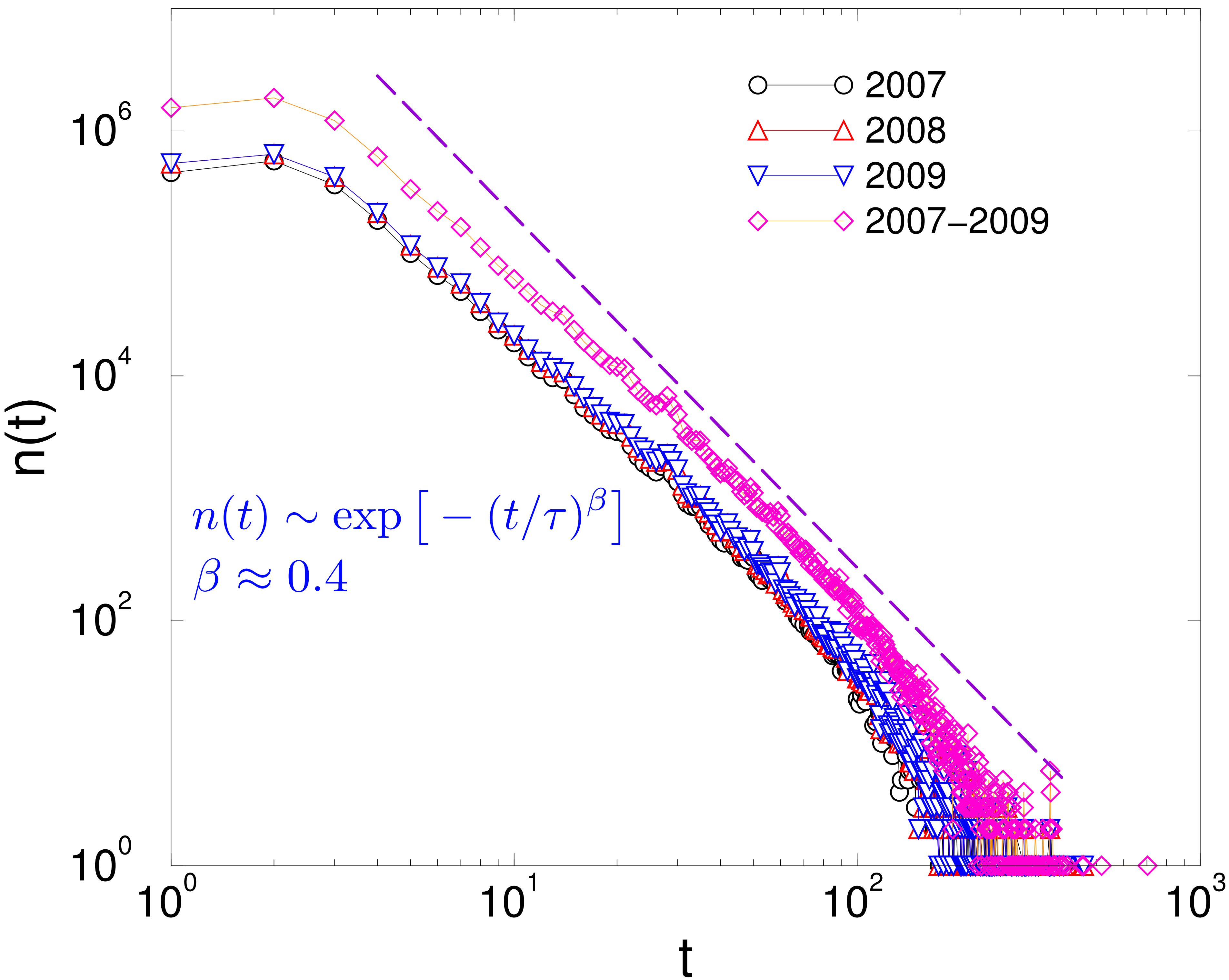
Immortality for

$$4Dk/v^2 \geq 1$$

Length of Hospitalizations

Berdahl, Bhat, Dufresne, SR

a tentative attempt to describe failure



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dead discharged

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model: *steady recovery*

sporadic setbacks

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$\approx 2\%$ $\approx 98\%$

dead treatment complication discharged

model: *steady recovery*

sporadic setbacks

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$\approx 2\%$ $\approx 98\%$

dead treatment complication discharged

model: *steady recovery*

sporadic setbacks

parameters: *recovery rate*

rate and extent of setbacks

Summary

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First-passage processes a basic and underlie many physiological phenomena

Idealized telomere dynamics model for immortality

Random walk insult/recovery model for hospitalization lengths