Are enzyme costs minimized in evolution?

Enzyme size, efficiency and turnover as a mean for better flux predictions in FBA

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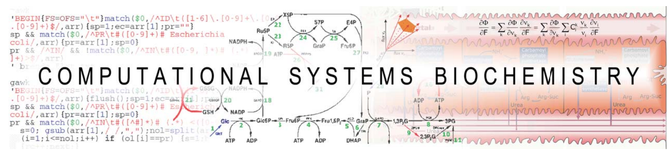


Summary. Presumably, the costs of enzymes are minimized in the course of evolution, e.g. enzymes are as small (to minimize the effort for protein synthesis), as efficient (to minimize the necessary amount of enzymes for the required catalyzed flux), and with as low a degradation rate (to minimize the need to replenish the enzyme) as possible. However, as other factors (e.g. effective regulation mechanisms) are critical for the cell's fitness it remains to be proved that costs have indeed an impact on the prevalence of enzymes throughout evolution.

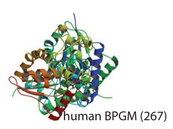
Here, the sequence lengths of the enzymes for central carbohydrate pathways is compared for selected classes in the tree of life in order to investigate the evolutionary preference of small enzymes. To assess the role of the different cost components the effect on the cost estimates is analyzed for two alternative pathways which yield glyceraldehyde phosphate and energy equivalants from activated glucose. As a concluding prospect, a flux-balance optimization procedure based on the minimization of required enzyme costs is presented.

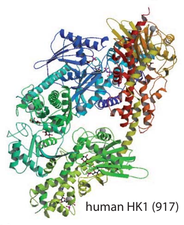
Sequence length (by active site)

- fits perfectly in cost concept: ***Investment***
- protein synthesis is major cell's energy consumer
- evolutionary pressure on protein size

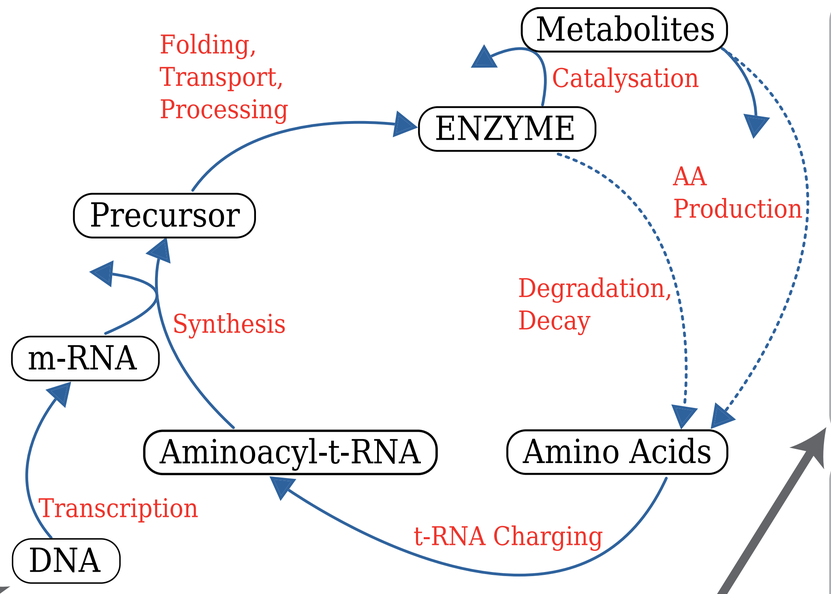
Constraints:

- Stable folding
- Protective sequences (Protrypsin)
- Coupling of free energy producing and consuming chemical reaction
- Membrane position
- Allosteric mechanisms
- Stable binding of prostethic groups
- Reglatory sites
- Reaction chamber (proteasome)





Data availability: perfect (uniprot+PDB)



Degradation rate

fits perfectly in cost concept: ***Depreciation***

Constraints:

- Degradation very important regulation mechanism
- Protein modification/aging inevitable (radicals)
- Elimination of faulty enzymes (Ubiquitin)

Data availability: very poor, only few studies (e.g. [4])

Efficiency (turnover number)

fits relatively well in cost concept: ***Productivity***

Constraints:

- Diffusion time
- Reaction mechanism

Problems:

- Depends on conditions
- Enzyme concentration and turnover not linear

Data availability: good (BRENDA) but large deviations

Cost function

$$\langle \text{cost} \rangle = \frac{\langle \text{chainlength} \rangle \ \langle \text{degradation} \rangle}{\langle \text{efficiency} \rangle \ \langle \text{specificity} \rangle}$$

Specificity (relative)

fits less well in cost concept: ***Intensity of Labour***

- turnover of alternative reactants reduces efficiency

Constraints:

- Binding of chemically similar substances inevitable
- Essential side functions (e.g. stowaways)

Problem:

- depends on concentrations of alternative substrates

Typical: tradeoff between specificity and efficiency

Data availability: mediocre (BRENDA)

Comparison of chain lengths

- Selected pathways, all species, data from KEGG [6].
- Hierarchic arithmetic average chain lengths with respect to KEGG 4-level taxonomy used.
- Percentage (+/–) of average chain lengths of first category with respect to second shown.
- Results support: *intensive evolutionary development correlates with shorter chains.*

Enzyme of first category is smaller … larger than enzyme of second category

Classes \ Reaction	Glc → Glc6P	Glc6P → Fru6P	Fru6P → Fru1,6P	Fru1,6P → Fru6P	Fru1,6P → GraP + DHAP	GraP → DHAP	GraP → 1,3PG	1,3PG → 3PG	2,3PG → 3PG	3PG → 2PG	2PG → PEP	PEP → Pyr	Pyr → Lac	Pyr → OAA	Pyr → Acetyl-CoA	OAA → Mal	Mal → Fum	Fum → Succ	Succ → Succ-CoA	Succ-CoA → AKG	AKG → ICit	ICit → Cit	Cit → Ac-CoA + OAA	Glc6P → bGlu6P	bGlu6P → Glc1,5LacP	Glc1,5LacP → 6PG	6PG → Ru5P	6PG → GraP + Pyr	X5P + R5P → GraP + S7P	GraP + S7P → Fru6P + E4P	Ru5P → X5P	Ru5P → R5P	R5P → PrPP
Pathway	Glycolysis													TCA										Pent-P ox				Pent-P non-ox				
Eukaryotes vs. Prokaryotes	14	31	82	-15	9	8	3	3	17	6	5	11	2	57	14	11	54	2	12	70	-3	6	44	-11	6	-3	33	-18	51	-39	6	9	16
Animals vs. Plants	-6	-15	53	-13	1	-11	-4	-18		-15	-5	-4	-4	-1	-4	-6	7	6	-2	-7	-3	-12	54	-15	-9	-14	-9		-11	-20	-8	-8	-16
Animals vs. Fungi	-2	-2	-5	-2	12	-1	3	-6		5	5	7	7	-5	5	-1	15	-4	-2	-3	-2	6	22	-2	5	-1	1		-2	-1	-4	22	-5
Animals vs. Protists	9	-15	18	-12	-1	-4	2	-12		12	-8	4	8	-5	1	-17	8	-2	1	-4	-3	-8	2	-15	-21	-37	-4		-9	-1	-3	25	-7
Plants vs. Fungi	5	15	-37	12	10	11	7	15		22	11	12	11	-3	10	6	7	-10	0	5	2	20	-21	15	15	15	11		10	24	4	33	13
Plants vs. Protists	16	0	-23	1	-2	8	6	8		32	-3	8	12	-4	5	-12	1	-8	3	3	1	5	-34	0	-13	-27	5		3	23	5	36	10
Fungi vs. Protists	10	-13	23	-10	-11	-3	-1	-6		8	-13	-3	1	-1	-5	-17	-6	2	3	-2	-1	-13	-17	-13	-25	-37	-5		-7	-1	1	2	-2
Vertebrates vs. Arthropods	31	-1	-4	-1	1	-8	-1	1		-35	36	0	-2	-11	6	1	4	-3	8	5	-1	-2	25	-1	0	-13	2		4	19	-1	31	-5
Vertebrates vs. Echinoderms	48	2	-5	-3	1	-1	-1			-40	-24	19	-2		-27	-1	-27	-1	-1	12	0	9	-24	2	35	-14			4	7	-1	-1	6
Vertebrates vs. Lancelets	39	-2	5		14	-2	-1	1		-51	15	66		-5	35	39	-4	-3	1	-29	-5	2	1	-2	-2	-16	3		4	-5	0	11	4
Mammals vs. Birds	-7	-6	1	-5	7	-3	14	4	3	2	0	-1	-1	0	3	-3	3	-21	-1	-3	1	-6	-27	-6		8	10		-10	17	-2	5	7
Mammals vs. Amphibians	-8	-6	-1	-5	6	-3	6	4	4	2	0	2	-2	49	1	-2		-7	20	-2	3	-9	4	-6	1		10		0	-2	-2	30	14
Mammals vs. Fishes	-10	-6	1	-4	6	-3	-1	4	4	2	-6	1	-2	0	3	0	-1	-5	3	-2	3	-6	4	-6	-2	138	4		0	-2	-2	11	18
Bacteria vs. Archaea		41	-2	27	4	14	-1	-1		-10	3	-1	1	43	26	4	1	-15	3	52	16	0	21	87			34	76	77	145	3	1	11
Protists vs. Prokaryotes	5	41	74	-11	14	7	-1	5		-6	11	5	-3	61	14	25	49	4	10	71	-3	5	64	-4	25	30	34		55	-42	5	7	16
Protists vs. Bacteria	5	20	76	-11	11	1	0	6		-1	10	5	-3	60	11	23	48	5	8	71	-10	5	61	-9	25	30	17		22	-43	4	6	10
Protists vs. Archaea		70	72	13	16	15	-1	5		-11	13	4	-2	129	40	28	49	-10	11	160	5	4	95	70			57		115	40	7	7	22

Cost comparison Glycolysis vs. Pentose phosphate pathway

- Glycolysis versus Pentose-phosphate
- Substrate: glucose-6-phosphate; product: glyceraldehyde phosphate
- Data drawn from KEGG [6], BRENDA [5], and [4].
- Four Cost estimates: flux only, plus chain lengths considered, plus turnover numbers considered, plus degradation considered
- Glycolysis cheaper — main factor: turnover numbers

Enzyme cost for the reaction is expensive … cheap

Reaction		flux f	chain length c	cf	turnover number n	cf/n	degrad. rate d	dcf/n
Glycolysis: 1 Glc6P + 1 ATP/ADP → 2 GraP								
GPI	Glc6P → Fru6P	1	558	558	2456	0.23	0.17	0.04
PFK	Fru6P → Fru1,6P	1	780	780	388	2.01	2.65	5.33
FBA	Fru1,6P → GraP + DHAP	1	364	364	393.1	0.93	1.62	1.5
TPI	GraP → DHAP	1	249	249	7512.5	0.03	0.17	0.01
$\sum$		4		1951		3.2		6.9
Pentose-phosphate: 1 Glc6P + 0.67 ATP/ADP → 1.67 GraP + 1 CO_2 + 2 NADPH/NADP								
GPI	Glc6P → bGlu6P	1	558	558	2456	0.23	0.17	0.04
G6PD	bGlu6P → Glc1,5LacP	1	515	515	428.1	1.2	1.09	1.32
PGLS	Glc1,5LacP → 6PG	1	258	258	(809)	0.32	(1)	0.32
PGD	6PG → Ru5P	1	483	483	15.9	30.43	0.24	7.33
PFK	Fru6P → Fru1,6P	0.67	780	520	388	1.34	2.65	3.56
FBA	Fru1,6P → GraP + DHAP	0.67	364	242.7	393.1	0.62	1.62	1
TPI	GraP → DHAP	0.67	249	166	7512.5	0.02	0.17	0.004
RPE	Ru5P → X5P	0.67	228	152	2609.6	0.06	(1)	0.06
rpiA	Ru5P → R5P	0.33	311	103.7	25	4.15	(1)	4.15
tkt1	X5P + R5P → GraP + S7P	0.33	626	208.7	23.5	8.89	(1)	8.89
tal	GraP + S7P → Fru6P + E4P	0.33	337	112.3	8.1	13.83	(1)	13.83
tkt2	X5P + E4P → Fru6P + GraP	0.33	596	198.7	34.5	5.76	(1)	5.76
$\sum$		8		3518		66.8		46.2

Using cost as an objective for FBA

- Adapatation of the flux minimization principle [3].
- Objective: absolute flux value multiplied by specific enzyme cost.
- Linear optimization problem., implemented in [2], see [1] for details.

$$\textbf{Minimize} \quad \sum_{i=1}^{n} c_i |v_i|$$

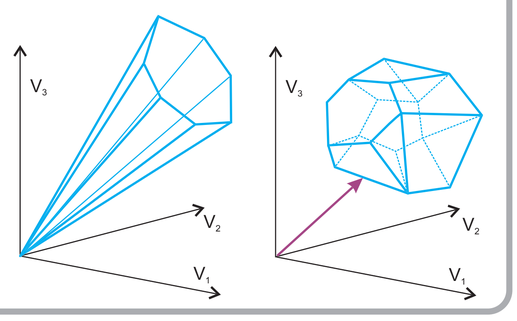
$$\textbf{Subject to} \quad \sum_{i=1}^{n} s_{ij} v_i = 0, \quad \forall j \quad \text{internal}$$

$$v_i = L_i, \quad \forall i \quad \text{target flux}$$

$(c_1, \ldots, c_n)$ enzyme costs vector

$(v_1, \ldots, v_n)$ flux vector

$(s_{ij})_{ij}$ stoichiometric matrix



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