

tional conditions that transform the problem of learning algebraic rules to the much simpler problem of learning to detect relevant coincidences within a spatiotemporal pattern. Our work suggests that even abstract algebraic rules can be grounded in concrete and basic notions such as spatial and temporal location and coincidence.

The representational and architectural conditions identified by the model are as follows.

1) There exist nodes that encode serial position within a sequence. Recent findings suggest that such nodes are biologically plausible (A. F. Carpenter *et al.*, Reports, 12 Mar., p. 1752).

2) The network can express bindings between a positional node and the item that occupies this position in a given sequence.

3) The bindings are expressed by means of temporal synchrony, that is, the occurrence of an item A in a particular position P in a sequence is coded by the synchronous activity of the cells encoding A and cells encoding P. There is considerable evidence that synchronization of neural activity might underlie the encoding of bindings (1, 5).

4) Nodes representing positional roles and items are interconnected by means of

recurrent connections mediated by intermediate (or hidden) layers of nodes.

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Likelihood of NIH Extramural Funding

Biomedical scientists need an estimate of the probability that their National Institutes of Health (NIH) research grant application will be funded. Previous letters in *Science* from our caucus (16 Dec. 1994, p. 1789; 7 July 1995, p. 13) provided the success rates of NIH grant requests. This information, specifically for unamended, unsolicited investigator-initiated R01 and

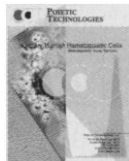
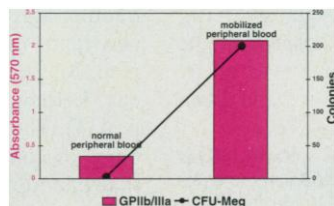
R29 (FIRST) NIH applications, is not readily available from the Internet or NIH publications, which usually report overall success rates of unamended as well as resubmitted new and renewal requests reviewed during a fiscal year. For example, NIH reported that for fiscal year (FY) 1998, about 31% of R01 requests were funded. These data included all new and renewal submissions, as well as solicited grant requests. We have updated the information on unsolicited new and renewal R01 and R29 applications for FY 1998 based on information provided by NIH (1).

Annual increases over inflation in federal NIH appropriations have raised success rates of new R01 plus R29 grant applications (that is, Type 1) from 14% (86% denied funding) in FY 1994 to 20% (80% denied funding) in FY 1998 (Table 1). There was no major change in total number of applications submitted. The table also shows the benefits of submitting or, if necessary, resubmitting, revised applications. Ultimately, about 36% of proposals were funded, a number difficult to establish accurately because the timing of submission of amended applications usually extends beyond the fiscal year, the period of reporting used by NIH.

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- Bone marrow mononuclear cells
- Bone marrow AC133⁺ cells
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- Cord blood CD19⁺ B cells
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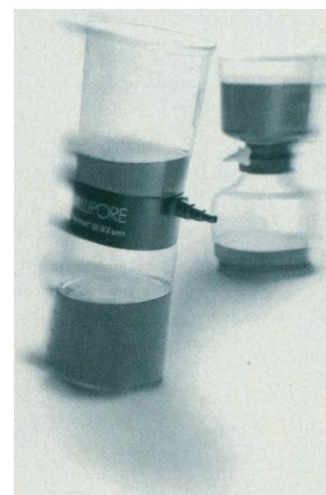
NIH institute	Unamended			First amendment		Second amendment	
	R01's (No.) Submitted	Funded	Success rate (%)	R01's (No.) Resubmitted	Funded	R01's (No.) Resubmitted	Funded
NIAAA	96	17	17.7	53	13	17	6
NIA	295	62	21.0	93	28	13	2
NIAID	623	145	23.3	190	75	50	26
NIAMS	252	43	17.1	68	22	15	4
NCI	1180	251	21.3	426	130	90	31
NIDA	199	39	19.6	74	20	32	16
NIDCD	118	14	11.9	47	12	15	4
NIDR	120	17	14.2	47	16	11	6
NIDDK	620	150	24.2	204	64	39	11
NIEHS	167	16	9.6	61	19	24	9
NEI	218	54	24.8	62	27	16	6
NIGMS	903	223	24.7	287	105	88	36
NICHHD	384	52	13.5	144	47	45	14
NHGRI	20	12	60.0	6	1	—	—
NHLBI	910	172	18.9	375	141	83	42
NIMH	403	53	13.2	184	73	46	20
NINR	45	10	22.2	20	3	8	3
NINDS	579	99	17.1	223	70	55	22
NCRR	26	7	26.9	7	5	1	1
=====							
TOTAL R01	7158	1436	20.1	2571	871	648	259
TOTAL R29	1179	248	21.0	463	158	103	45
FY 1998	8337	1684	20.2	3034	1029	751	304
=====							
TOTAL R01	6882	1191	17.3				
TOTAL R29	1343	293	21.8				
FY 1997	8225	1484	18.0				
=====							
TOTAL R01	6876	888	12.9				
TOTAL R29	1260	241	19.1				
FY 1994	8136	1129	13.9				

Table 1. Success rates for fiscal year 1998 of new, unsolicited, competing R01 and R29 research project grant applications (Type 1), as initially submitted (unamended), and after first and second revisions (amendments). The average success rates for first and second resubmissions were 33.9% and 40.0% for R01 applications, and 34.1% and 43.7% for R29 applications, respectively. Data from previous years included for comparison (4).

The average annual direct plus indirect cost of a funded Type 1 grant was about \$228,000, whereas the mean proposed budget for all such applications as originally submitted was \$274,000.

In a policy statement (2), our caucus previously recommended doubling the NIH budget to take advantage of the enormous opportunities now at hand to advance human health and quality of life. In addition, major economic benefits for our biotechnology,

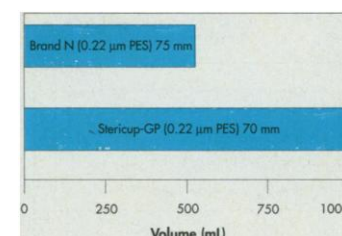
pharmaceutical, and chemical industries have arisen from new basic research. Excellent research ideas, highly lauded by peer-review committees, should not be denied funding or delayed sometimes by years, because each revision usually takes at least 9 to 12 months. Further efforts are required to reduce this delay. Grant reviewers have been impressed by the increasingly high quality of proposals over the years, probably because severe competition has all but eliminated



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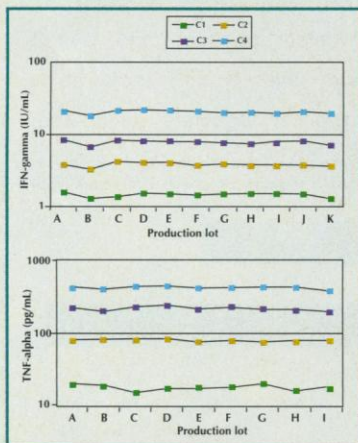
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clearly poor-quality applications. Although we are gratified that the success rate of unamended unsolicited R01 applications has increased over time, we remain committed to and still advocate funding half of peer-recommended applications. A doubling of the NIH budget over 5 years, as initiated by the 15% rise provided for FY 1999, should boost the success rate to more appropriate levels.

For renewal requests (Type 2), NIH states that 49% have been funded in FY 1998 without revision, compared with 37% in FY 1994. However, these research investigations have previously passed stringent peer review and are in full operation, and now 51% are being interrupted or terminated.

Because only limited time may have been available to achieve publishable results, the discontinuation of such programs, after the low success rate for first-time submissions, can cause major disruptions of research. Delays in funding can stop momentum, break up highly specialized teams of scientists dependent on uninterrupted support, and slow attainment of scientific breakthroughs. The fiscal hiatus has destroyed professional careers; lack of funding has led to denial of tenure (3) and academic dismissal. We need more of our well-trained professional talents to continue their scientific productivity. Desirability

of a scientific career should not be diminished in this way if we wish to recruit outstanding new candidates. For all these reasons, we urge that sufficient funds be provided to minimize all-too-costly interruptions in funding, with increasing availability of bridge support, for Type 2 renewal applications, especially for those close to the pay line.

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Overlooked Control

A serious technical oversight in some molecular regulation studies is occurring at an increasing rate. The tetracycline (tet)-inducible gene expression system has become a commonly used approach to experimenter-controlled expression of genes for functional evaluation in mammalian cells (1). There are two controls required for sound interpretation of cellular effects that occur when a "tet-inducible" gene is activated. The first control is the off-condition for the evaluated gene. The second is the on-condition for control cells derived with the tet-repressor-VP16 transactivator protein, but with an empty tet-operator vector. Invariably, this essential control is omitted. Of 12 surveyed recent reports using tet-inducible systems (2-13), only one reported a control of this type (8).

Removal of tetracycline or addition of doxycycline to induce test gene expression may appear to be otherwise innocuous events. However, they unleash the activity of a potent gene transactivator (14). Although the tet-repressor-VP16 fusion protein has a high affinity for the tet-operators, nothing prevents it from binding at other gene loci

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