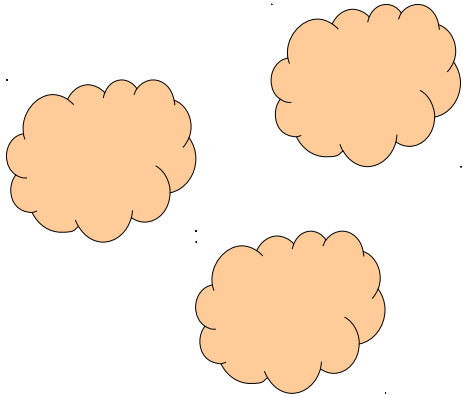


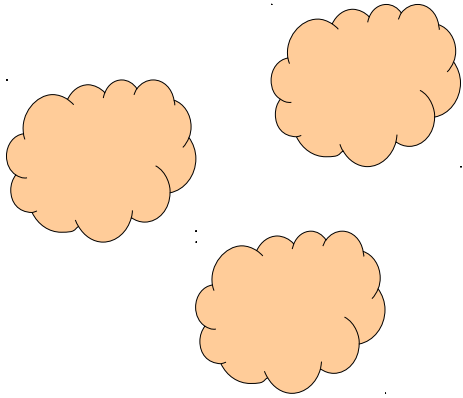
# Simulating the effects of anticoagulant drugs on blood clotting dynamics

Alexey Goltsov, Gregory Goltsov, Adam Sampson  
University of Abertay Dundee

platelets in  
bloodstream

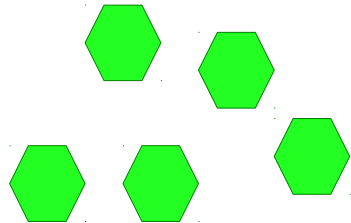
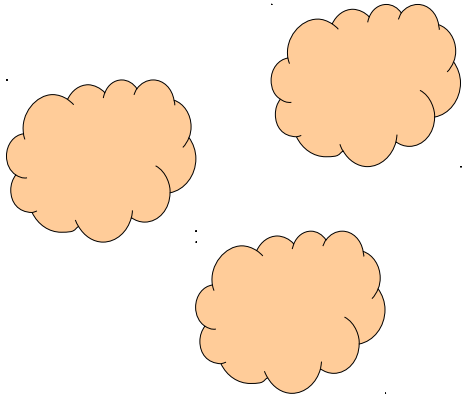


platelets in  
bloodstream



damaged tissue

platelets in  
bloodstream



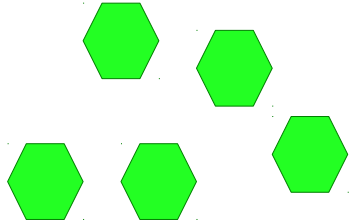
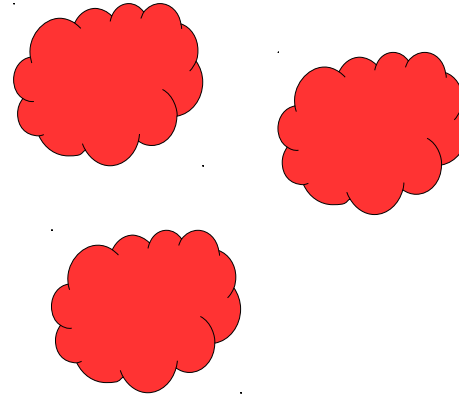
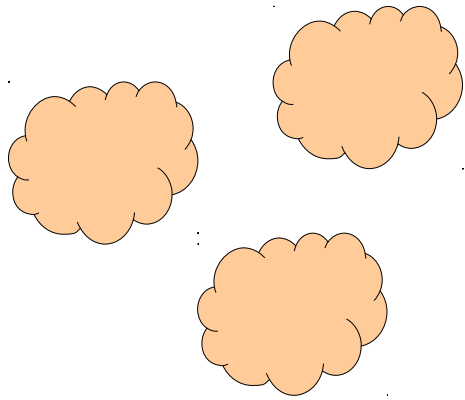
damaged tissue  
emits clotting factors



platelets in  
bloodstream

platelets become  
sticky

chemical  
signalling

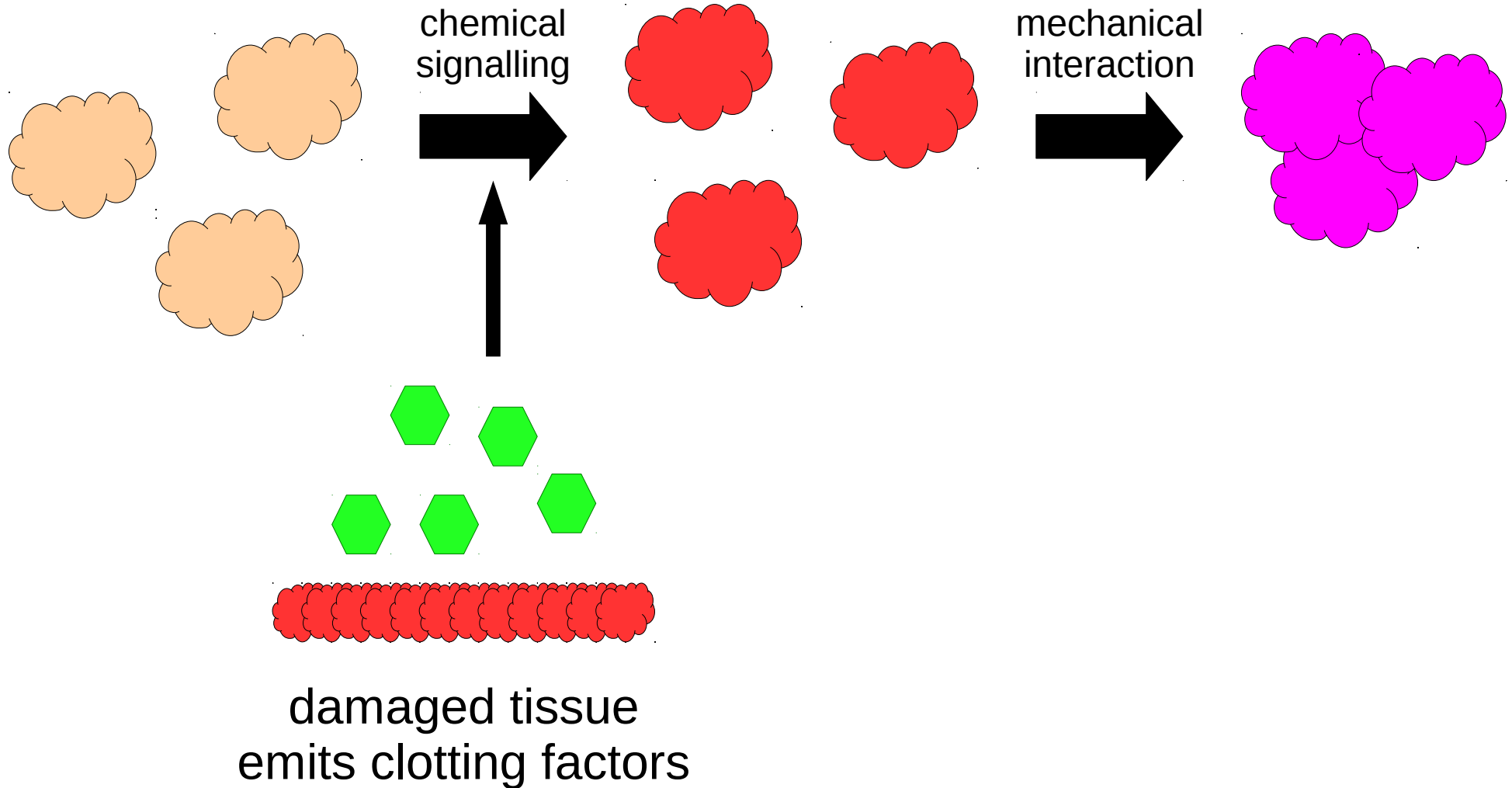


damaged tissue  
emits clotting factors

platelets in  
bloodstream

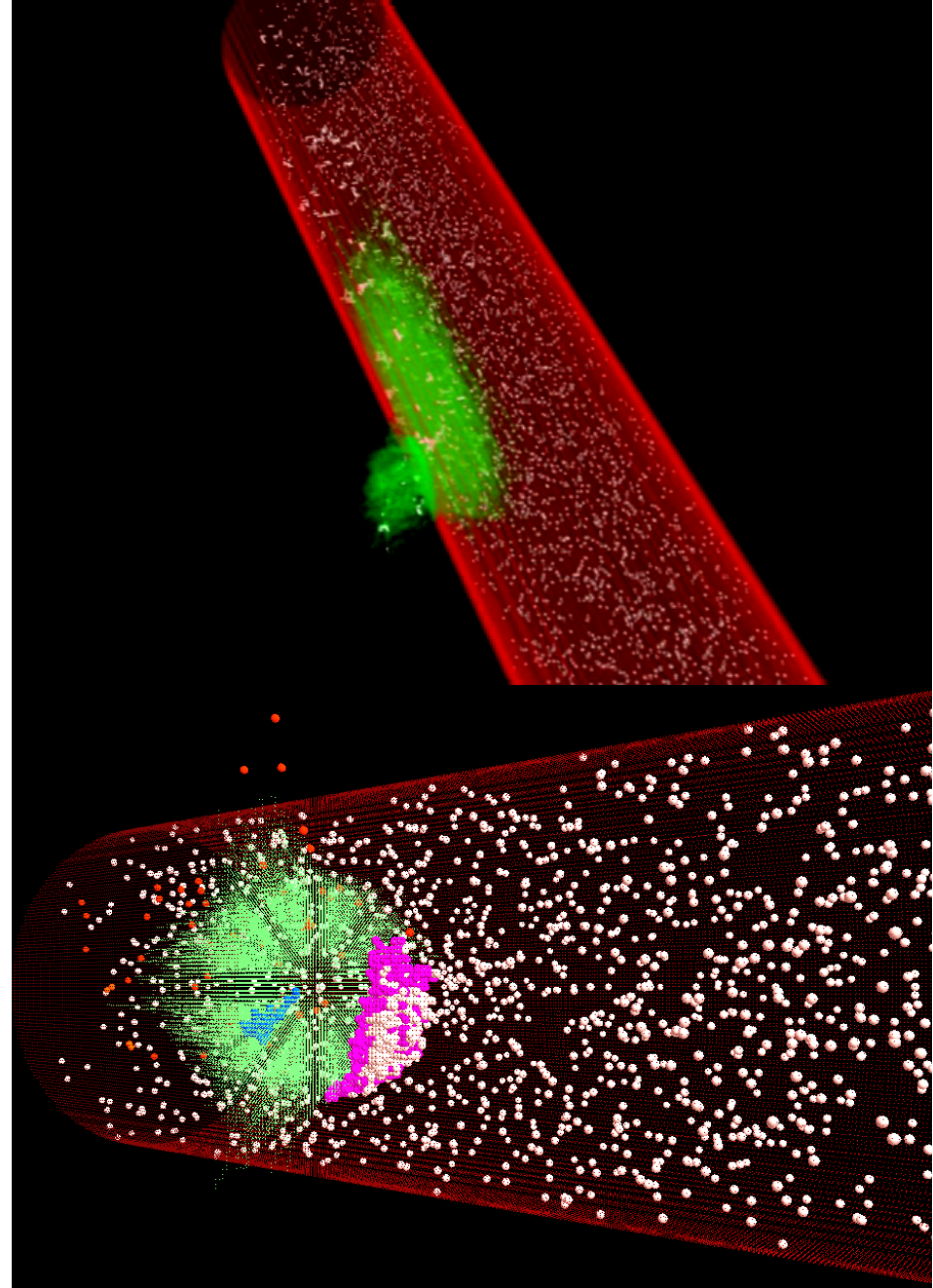
platelets become  
sticky

clots form



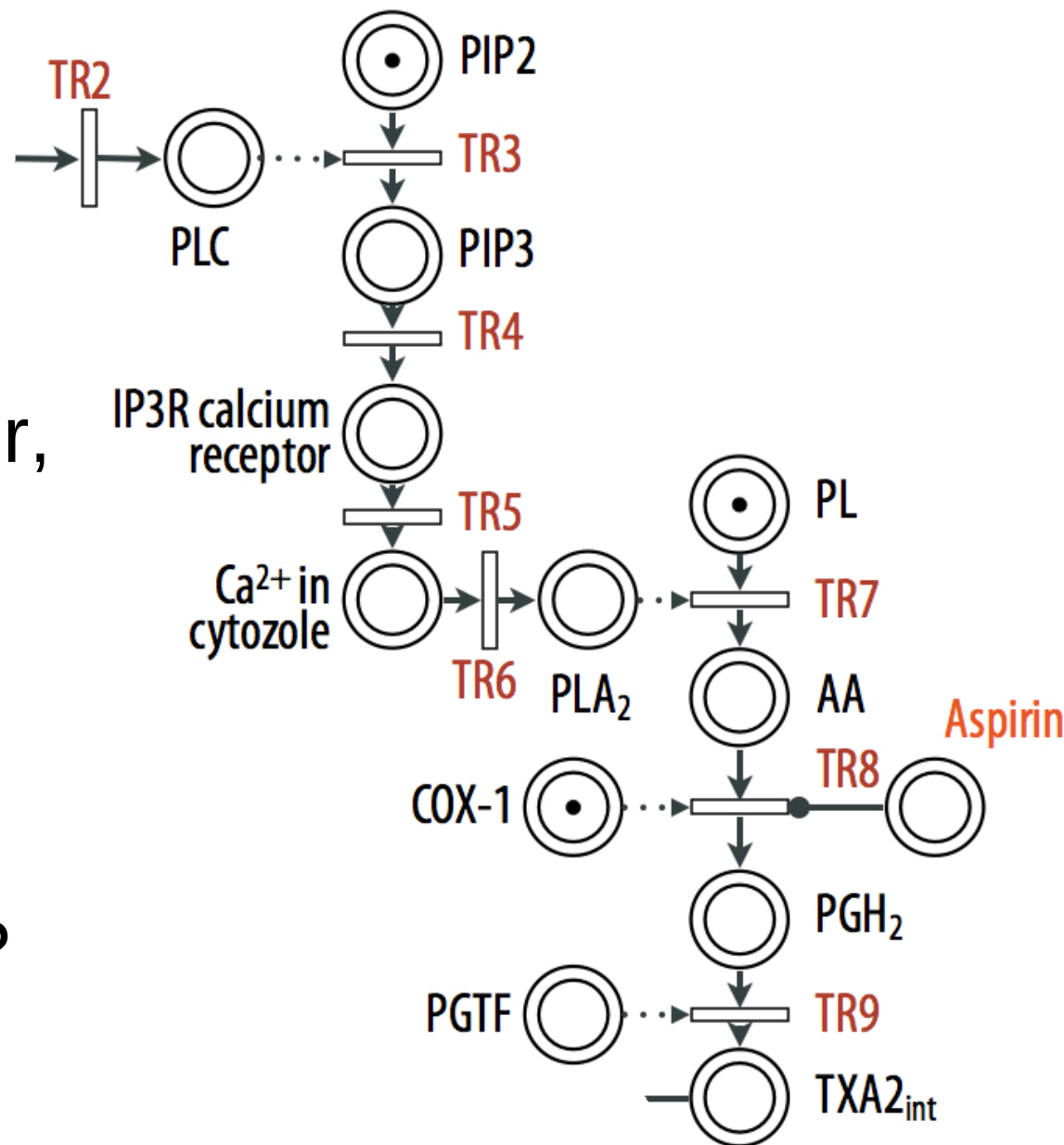
- This process doesn't always work properly
  - **Excessive** clotting – e.g. thromboembolisms
  - **Insufficient** clotting
- To treat these problems, we use drugs to change the behaviour of platelets' **signalling networks**
  - ... such as aspirin
  - ... or specialised anticoagulants
  - ... or – more interestingly – **combinations** of the above

- 2008: Carl Ritson et al. built a large-scale simulator of **artificial** platelets for the **TUNA** project; simple physics, but no real behaviour
- 2010: ATS rebuilt simulator using **CoSMoS** tech; same behaviour, but supports interactive use





- Meanwhile, AG was modelling platelet signalling under the effects of various drugs; good behaviour, but no physics
- Both the **signalling** and the **physics** matter!
- Combine the models?



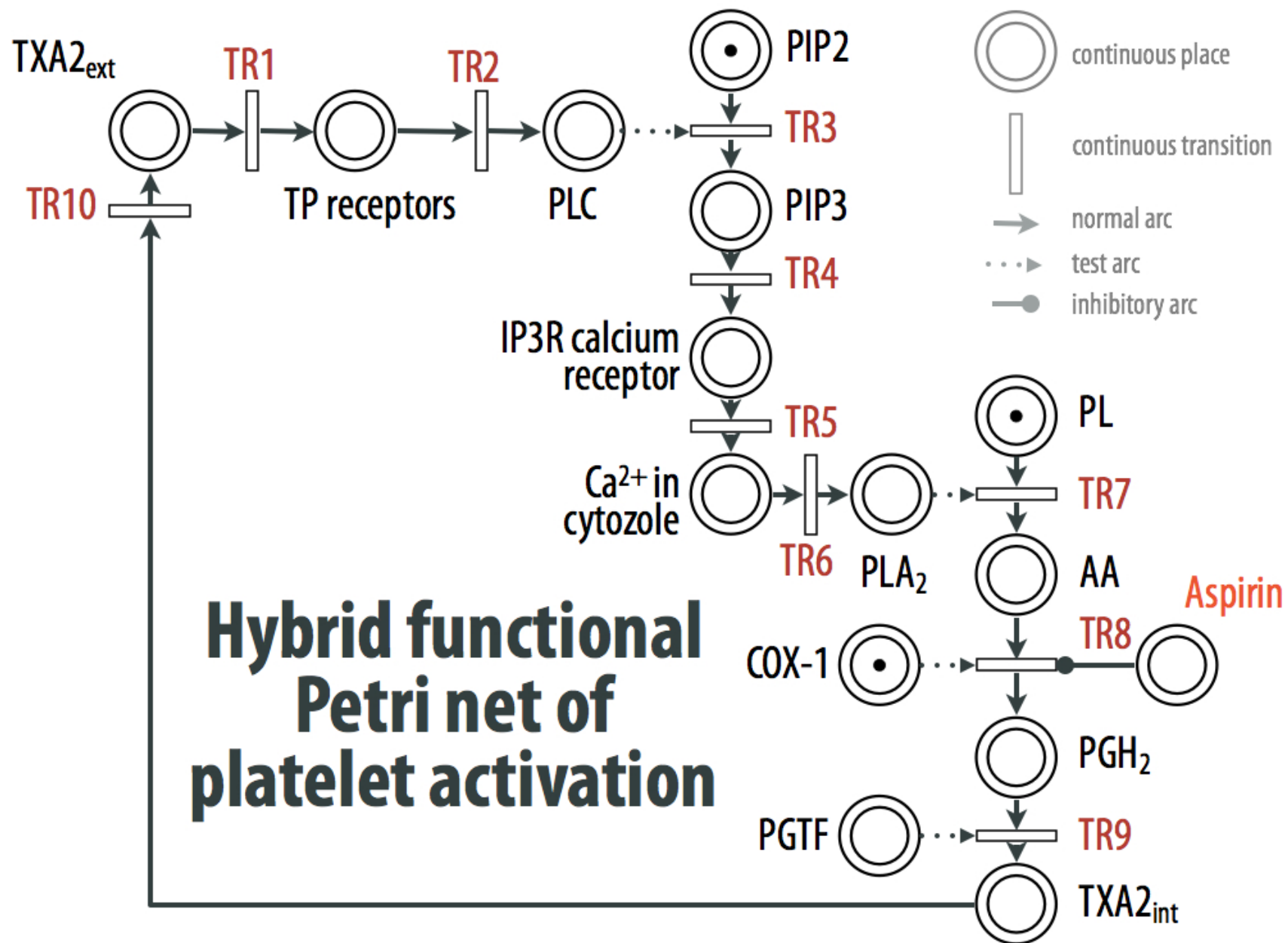




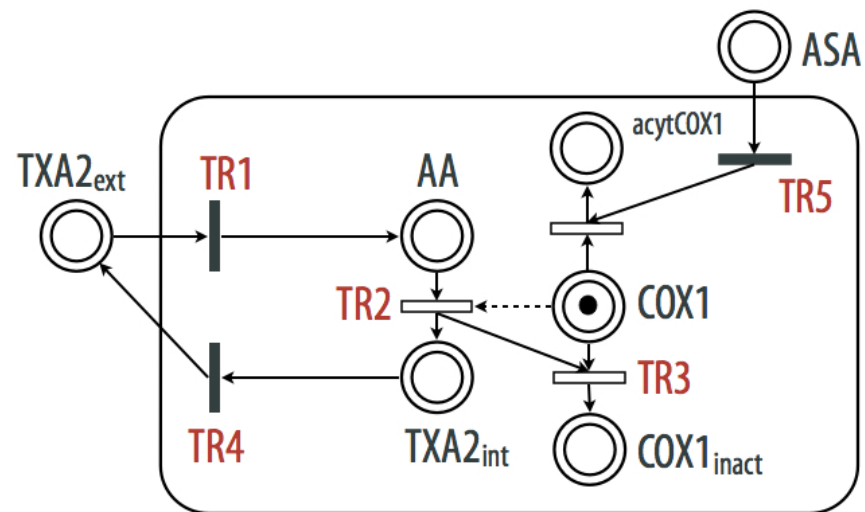
So GG applied for –  
and was awarded –  
a 2011 Nuffield bursary



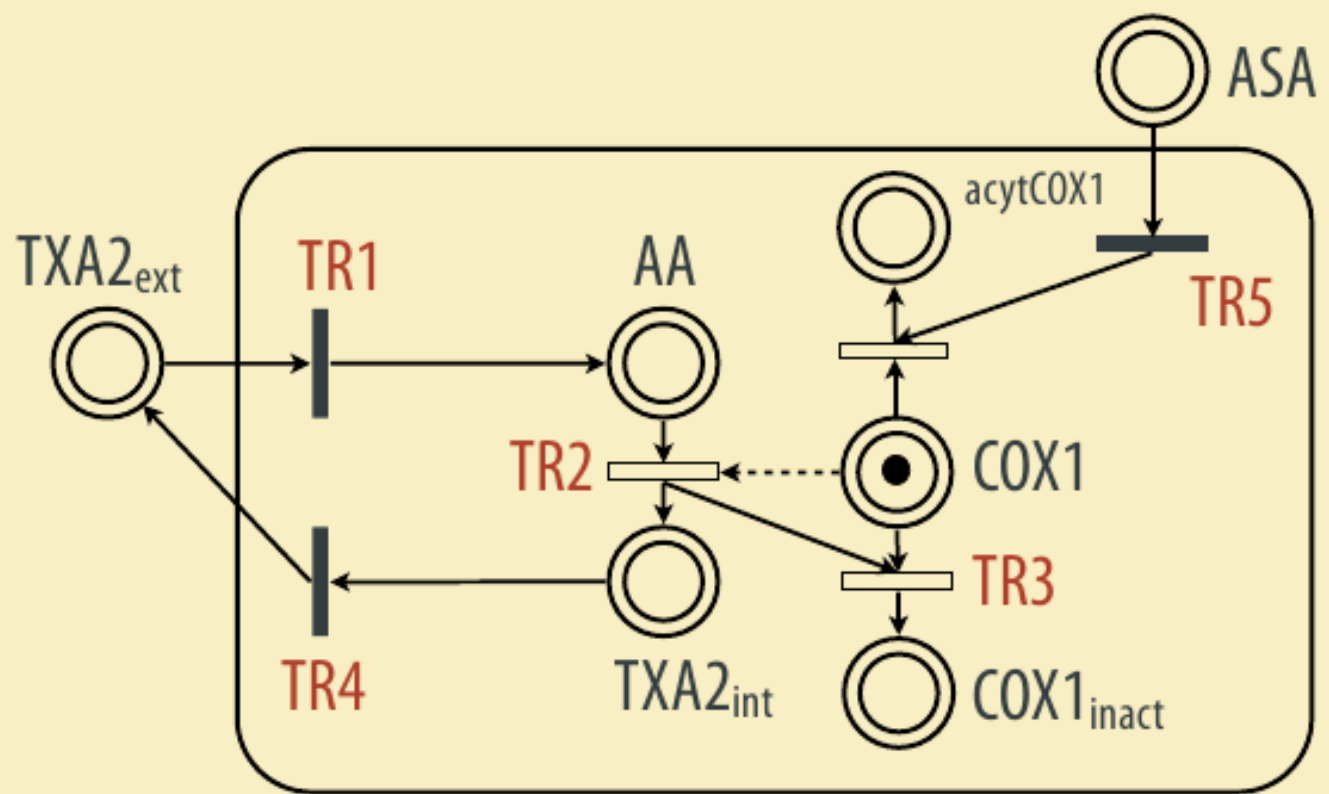
- Identify signalling metamodel: **hybrid Petri nets**
  - ... hybrid because they have **continuous** quantities rather than **discrete** tokens
  - ... but the graphical language is convenient!
- Identify an appropriate (subset) signalling model based on AG's existing one
- Define a **domain-specific language** for hybrid Petri nets so we can automatically generate the code AG wrote by hand...
- Give each cell in the simulator its own Petri net







# Model



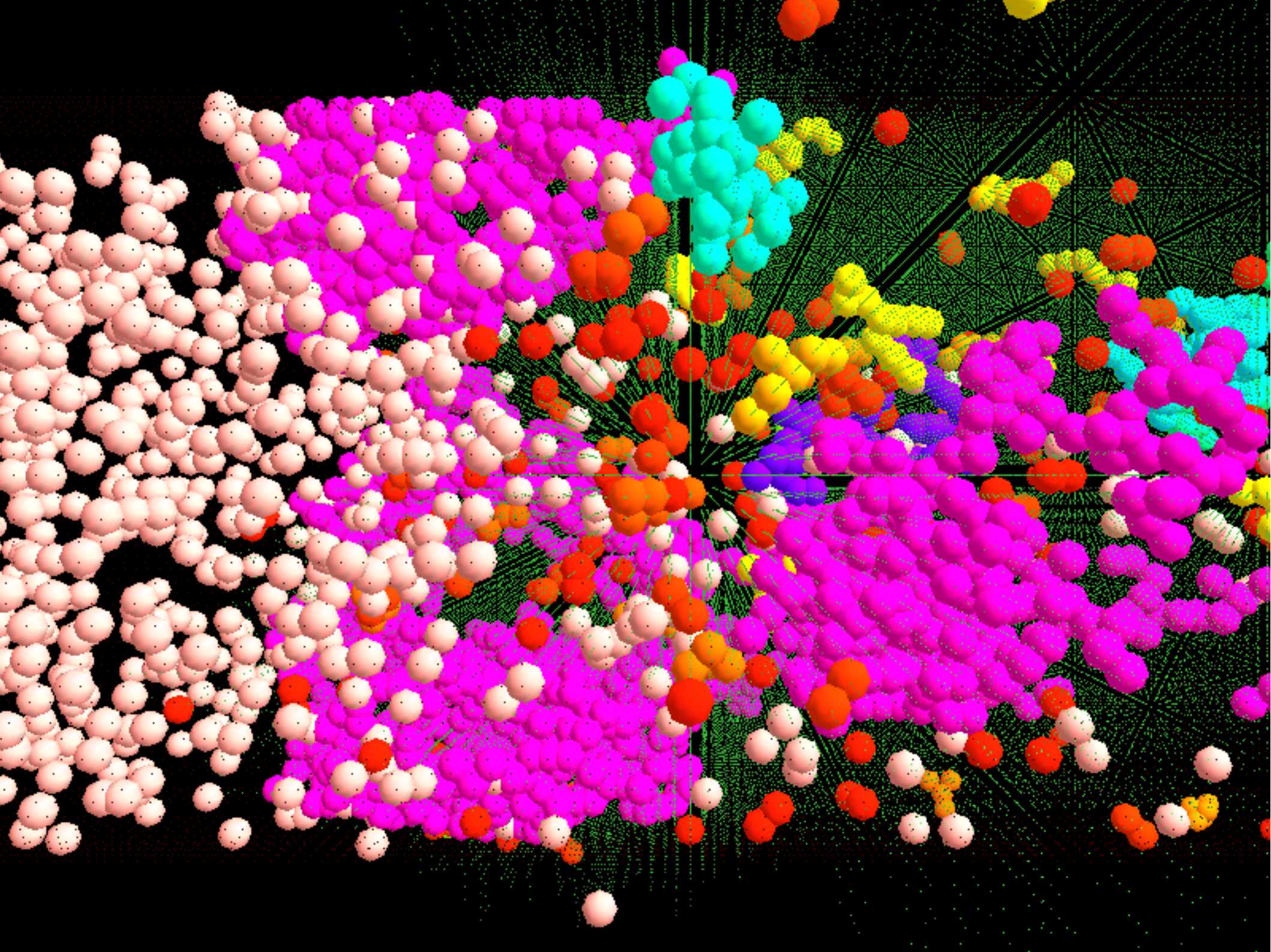
# DSL

DOMAIN-  
SPECIFIC  
LANGUAGE

```
// Place(name, initial_concentration)
NodePtr txa2_ext (new Place("TXA2_ext"
NodePtr aa      (new Place("AA"
NodePtr cox1    (new Place("COX1"
NodePtr txa2_int (new Place("TXA2_int"

// Transition(name, substrate, product,
NodePtr tr1 (new Transition("TR1", tr1_
NodePtr tr2 (new Transition("TR2", tr2_
NodePtr tr3 (new Transition("TR3", tr3_
```

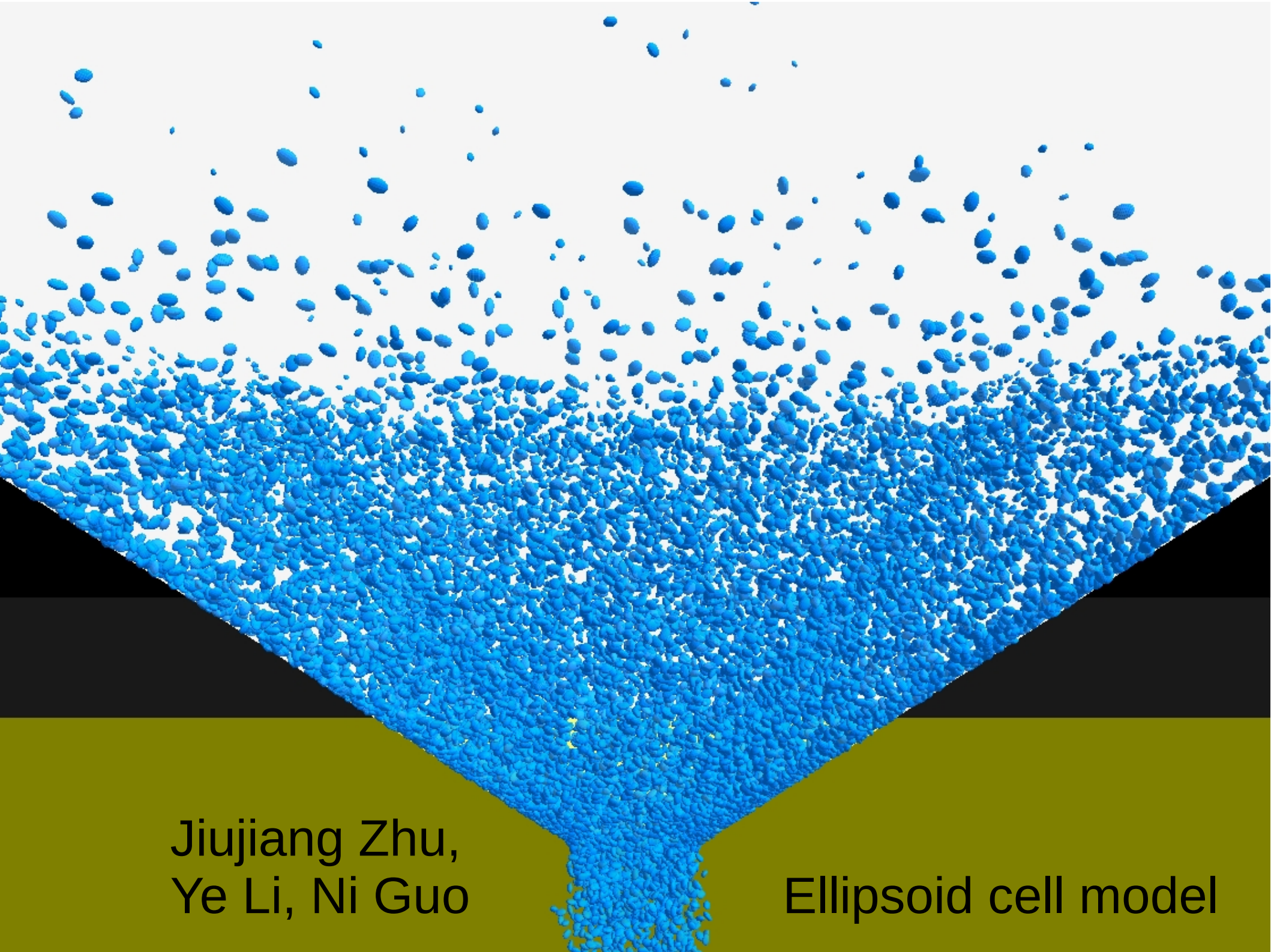




- Success!
- ... that is, the **technology** works; we haven't yet calibrated the combined model
- Platelets can now **amplify** the damage signalling: you don't need to emit (unrealistically) large signals into the bloodstream any more
- Can adjust **signalling** model parameters in real time and see the **physical** effects

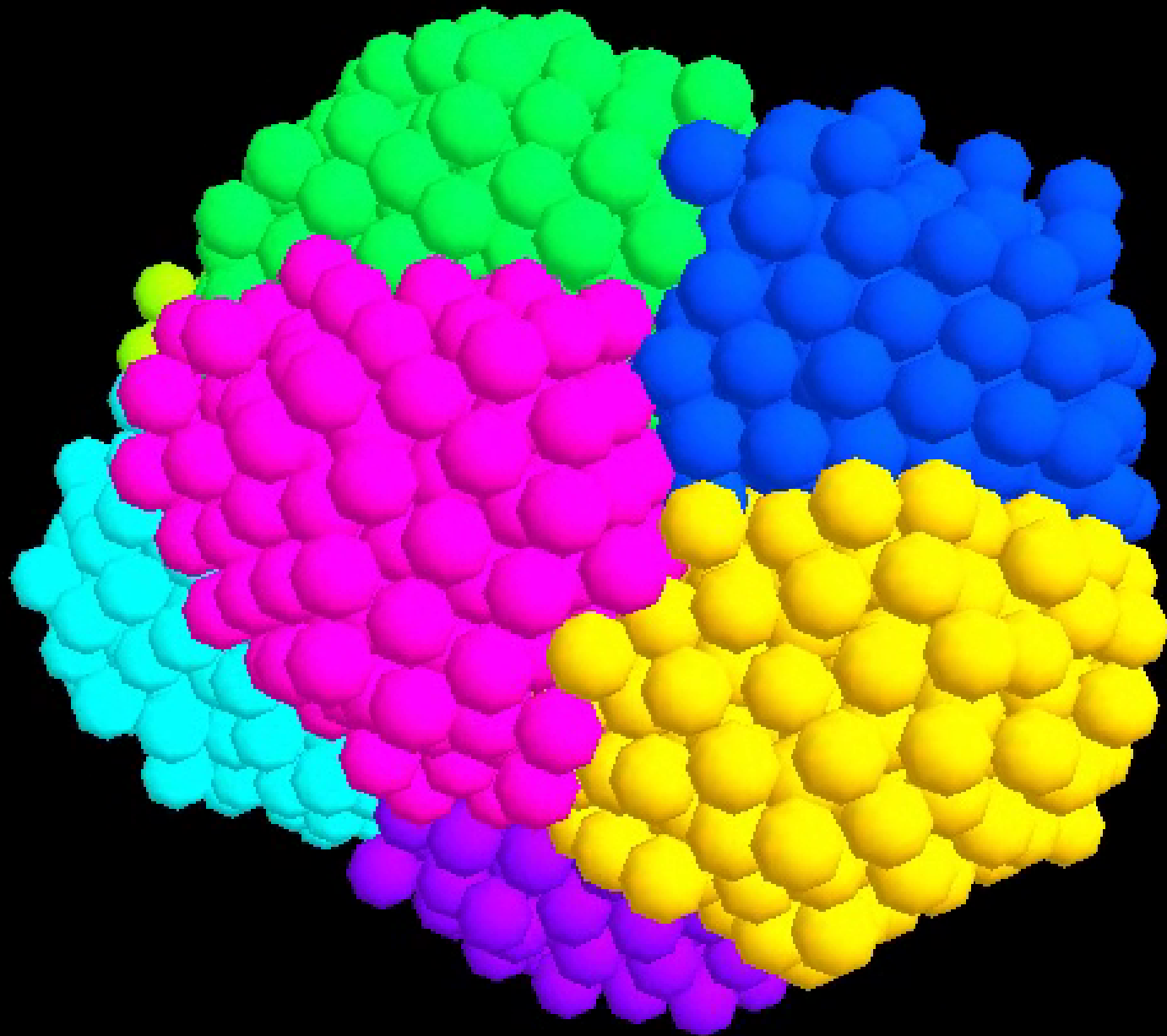


- Where next? Better metamodel tool support?
- We actually want to use this for **cancer**, rather than blood clotting – same modelling technologies, but more complex problems
- ... for example, helping to design drugs that affect tumour morphology when growing **into tissue** – less invasive, easier to remove
- For this, we need a more sophisticated physical model too...



Jiujiang Zhu,  
Ye Li, Ni Guo

Ellipsoid cell model



Tim Newman, Dundee  
ScEM finite-element cell model



## ats@aries:-

top - 12:34:11 up 268 days, 21:35, 3 users, load average: 26.06, 26.03, 24.78  
 Tasks: 370 total, 21 running, 348 sleeping, 0 stopped, 1 zombie  
 Cpu(s): 47.3%us, 1.4%sy, 0.0%ni, 51.3%id, 0.0%wa, 0.0%hi, 0.0%si, 0.0%st  
 Mem: 12322180k total, 4474268k used, 7847912k free, 104456k buffers  
 Swap: 23437304k total, 5666576k used, 17770728k free, 452188k cached

PID	USER	PR	NI	VIRT	RES	SHR	S	%CPU	%MEM	TIME+	COMMAND
31816	tg93	20	0	1321m	127m	9524	S	119	1.1	0:05.75	java
31795	tg93	20	0	1347m	130m	9528	S	104	1.1	0:06.64	java
31643	tg93	20	0	1325m	491m	9576	S	104	4.1	0:25.68	java
31695	tg93	20	0	1367m	478m	9576	S	101	4.0	0:25.88	java
28710	ats	20	0	161m	8984	6556	R	100	0.1	6:11.71	cellmodel
28711	ats	20	0	161m	8732	6504	R	100	0.1	7:22.30	cellmodel
31665	tg93	20	0	1437m	440m	9576	S	68	3.7	0:23.82	java
28708	ats	20	0	161m	10m	8712	R	40	0.1	3:43.59	cellmodel
28709	ats	20	0	161m	10m	8720	R	40	0.1	5:02.43	cellmodel
31756	tk243	20	0	280m	112m	924	R	7	0.9	0:00.82	R
31760	tk243	20	0	280m	113m	924	R	7	0.9	0:00.81	R
31750	tk243	20	0	280m	112m	924	R	6	0.9	0:00.84	R
31753	tk243	20	0	280m	112m	924	R	6	0.9	0:00.81	R
31754	tk243	20	0	280m	112m	924	R	6	0.9	0:00.81	R
31757	tk243	20	0	280m	112m	924	R	6	0.9	0:00.81	R
31758	tk243	20	0	280m	113m	924	R	6	0.9	0:00.81	R
31761	tk243	20	0	280m	113m	924	R	6	0.9	0:00.81	R

## ats@auriga:-

top - 12:34:12 up 282 days, 20:55, 2 users, load average: 21.96, 22.34, 18.93  
 Tasks: 320 total, 5 running, 314 sleeping, 0 stopped, 1 zombie  
 Cpu(s): 78.8%us, 16.2%sy, 0.0%ni, 5.0%id, 0.0%wa, 0.0%hi, 0.0%si, 0.0%st  
 Mem: 12324360k total, 5726552k used, 6597808k free, 104880k buffers  
 Swap: 23437304k total, 1031816k used, 22405488k free, 699588k cached

PID	USER	PR	NI	VIRT	RES	SHR	S	%CPU	%MEM	TIME+	COMMAND
2495	tg93	20	0	1336m	169m	9560	S	166	1.4	0:11.28	java
2470	tg93	20	0	1317m	153m	9560	S	141	1.3	0:10.54	java
2240	tg93	20	0	1434m	458m	9576	S	127	3.8	0:26.19	java
2297	tg93	20	0	1362m	432m	9576	S	111	3.6	0:25.56	java
2214	tg93	20	0	1354m	528m	9576	S	106	4.4	0:27.69	java
2158	tg93	20	0	1401m	491m	9576	S	99	4.1	0:25.98	java
2374	tg93	20	0	1368m	347m	9576	S	99	2.9	0:21.42	java
27288	ats	20	0	161m	7716	5236	R	98	0.1	7:22.41	cellmodel
27285	ats	20	0	161m	7544	5240	R	95	0.1	7:22.15	cellmodel
2303	tg93	20	0	1400m	449m	9576	S	93	3.7	0:25.21	java
2183	tg93	20	0	1351m	516m	9576	S	88	4.3	0:26.39	java
2260	tg93	20	0	1409m	500m	9576	S	86	4.2	0:28.68	java
2339	tg93	20	0	1377m	505m	9576	S	79	4.2	0:26.81	java
27287	ats	20	0	161m	7660	5260	R	49	0.1	4:22.45	cellmodel
27286	ats	20	0	161m	7660	5264	R	49	0.1	5:06.69	cellmodel
1015	ats	20	0	10996	1400	912	R	1	0.0	0:00.48	top
1602	sgeadmin	20	0	98620	2976	1764	S	1	0.0	383:01.39	sge_execd

## ats@capricorn:-

top - 12:34:12 up 24 days, 1:32, 1 user, load average: 21.82, 22.07, 18.51  
 Tasks: 283 total, 5 running, 278 sleeping, 0 stopped, 0 zombie  
 Cpu(s): 71.7%us, 16.7%sy, 0.0%ni, 11.5%id, 0.1%wa, 0.0%hi, 0.0%si, 0.0%st  
 Mem: 12324360k total, 2670192k used, 9654168k free, 102152k buffers  
 Swap: 23437304k total, 573160k used, 22864144k free, 382108k cached

PID	USER	PR	NI	VIRT	RES	SHR	S	%CPU	%MEM	TIME+	COMMAND
29775	tg93	20	0	1360m	219m	9564	S	203	1.8	0:14.88	java
29771	tg93	20	0	1362m	241m	9564	S	180	2.0	0:15.67	java
29620	tg93	20	0	1412m	492m	9576	S	126	4.1	0:27.96	java
29534	tg93	20	0	1390m	490m	9576	S	119	4.1	0:28.74	java
29600	tg93	20	0	1421m	501m	9576	S	117	4.2	0:28.76	java
21547	ats	20	0	161m	7664	5272	R	97	0.1	5:55.73	cellmodel
21550	ats	20	0	161m	7532	5304	R	92	0.1	5:53.44	cellmodel
21549	ats	20	0	161m	7656	5248	R	87	0.1	5:55.56	cellmodel
21548	ats	20	0	161m	7940	5520	R	86	0.1	5:57.72	cellmodel
2004	sgeadmin	20	0	97596	3968	1904	S	0	0.0	21:46.35	sge_execd
2481	root	-2	0	3928	1880	1580	S	0	0.0	4:12.12	watchdog
21543	ats	20	0	43876	1436	892	S	0	0.0	0:00.32	orted
28292	ats	20	0	10996	1396	912	R	0	0.0	0:00.40	top
1	root	20	0	8352	620	584	S	0	0.0	0:10.43	init
2	root	20	0	0	0	0	S	0	0.0	0:00.12	kthreadd
3	root	RT	0	0	0	0	S	0	0.0	0:00.88	migration/0
4	root	20	0	0	0	0	S	0	0.0	0:02.12	ksoftirqd/0

## ats@cephus:-

top - 12:34:11 up 282 days, 19:42, 1 user, load average: 22.46, 22.48, 18.90  
 Tasks: 345 total, 5 running, 332 sleeping, 0 stopped, 2 zombie  
 Cpu(s): 77.1%us, 14.5%sy, 0.0%ni, 8.4%id, 0.0%wa, 0.0%hi, 0.0%si, 0.0%st  
 Mem: 12322180k total, 5007684k used, 7314496k free, 99792k buffers  
 Swap: 23437304k total, 3190788k used, 20246516k free, 395264k cached

PID	USER	PR	NI	VIRT	RES	SHR	S	%CPU	%MEM	TIME+	COMMAND
25073	tg93	20	0	1393m	153m	9596	S	181	1.3	0:10.34	java
24919	tg93	20	0	1372m	450m	9620	S	127	3.7	0:25.22	java
24911	tg93	20	0	1389m	413m	9620	S	123	3.4	0:23.46	java
24754	tg93	20	0	1408m	509m	9620	S	120	4.2	0:26.04	java
24837	tg93	20	0	1475m	418m	9620	S	117	3.5	0:23.45	java
24783	tg93	20	0	1324m	441m	9620	S	113	3.7	0:23.34	java
25076	tg93	20	0	1326m	148m	9572	S	101	1.2	0:07.35	java
17387	ats	20	0	161m	7632	5228	R	100	0.1	7:27.37	cellmodel
17390	ats	20	0	161m	7496	5264	R	100	0.1	7:28.02	cellmodel
24892	tg93	20	0	1399m	479m	9620	S	90	4.0	0:25.35	java
24863	tg93	20	0	1418m	526m	9620	S	88	4.4	0:28.04	java
24961	tg93	20	0	1404m	345m	9620	S	87	2.9	0:19.89	java
24809	tg93	20	0	1399m	399m	9620	S	47	2.8	0:20.27	java
17389	ats	20	0	161m	7504	5268	R	35	0.1	4:24.06	cellmodel
17386	ats	20	0	161m	7632	5284	R	34	0.1	3:52.72	cellmodel
24323	ats	20	0	10996	1424	908	R	1	0.0	0:00.24	top
2069	root	-2	0	3928	1880	1580	S	0	0.0	58:21.01	watchdog

## ats@corona:-

top - 12:34:12 up 282 days, 20:22, 1 user, load average: 23.70, 22.86, 19.36  
 Tasks: 309 total, 5 running, 304 sleeping, 0 stopped, 0 zombie  
 Cpu(s): 75.8%us, 15.8%sy, 0.0%ni, 8.0%id, 0.4%wa, 0.0%hi, 0.0%si, 0.0%st  
 Mem: 12322180k total, 2388628k used, 9933552k free, 99424k buffers  
 Swap: 23437304k total, 1278036k used, 22159268k free, 399788k cached

PID	USER	PR	NI	VIRT	RES	SHR	S	%CPU	%MEM	TIME+	COMMAND
20755	tg93	20	0	1396m	280m	9564	S	186	2.3	0:16.05	java
20808	tg93	20	0	1356m	280m	9564	S	175	2.3	0:16.09	java
20870	tg93	20	0	1336m	162m	9548	S	104	1.4	0:08.19	java
20914	tg93	20	0	1363m	165m	9548	S	104	1.4	0:07.89	java
20781	tg93	20	0	1395m	185m	9552	S	102	1.5	0:10.00	java
20840	tg93	20	0	1400m	161m	9548	S	101	1.3	0:08.63	java
13579	ats	20	0	161m	7664	5256	R	100	0.1	7:18.47	cellmodel
13581	ats	20	0	161m	7660	5256	R	100	0.1	7:25.16	cellmodel
15522	tk243	20	0	3512m	948	800	S	100	0.0	20875:40	java
20858	tg93	20	0	1359m	151m	9548	S	99	1.3	0:08.42	java
20911	tg93	20	0	1396m	136m	9528	S	96	1.1	0:07.45	java
20927	tg93	20	0	1337m	144m	9528	S	92	1.2	0:07.47	java
13580	ats	20	0	161m	7668	5260	R	49	0.1	4:53.57	cellmodel
13582	ats	20	0	161m	7560	5260	R	49	0.1	4:58.44	cellmodel
20751	tg93	20	0	9312	1404	1172	S	1	0.0	0:00.06	bash
1974	sgeadmin	20	0	97600	3172	1876	S	0	0.0	319:31.57	sge_execd
20281	ats	20	0	10996	1392	908	R	0	0.0	0:00.23	top

## ats@leo:-

top - 12:34:11 up 280 days, 2:13, 1 user, load average: 20.87, 22.19, 18.83  
 Tasks: 294 total, 5 running, 288 sleeping, 0 stopped, 1 zombie  
 Cpu(s): 73.9%us, 20.3%sy, 0.0%ni, 5.8%id, 0.0%wa, 0.0%hi, 0.0%si, 0.0%st  
 Mem: 12322180k total, 1950384k used, 10371796k free, 103284k buffers  
 Swap: 23437304k total, 487775k used, 22949528k free, 394712k cached

PID	USER	PR	NI	VIRT	RES	SHR	S	%CPU	%MEM	TIME+	COMMAND
23745	tg93	20	0	1353m	278m	9508	S	207	2.3	0:14.41	java
23880	tg93	20	0	1324m	149m	9592	S	182	1.2	0:08.50	java
23620	tg93	20	0	1404m	192m	9592	S	181	1.6	0:12.44	java
23775	tg93	20	0	1333m	177m	9580	S	172	1.5	0:10.58	java
23793	tg93	20	0	1366m	156m	9596	S	127	1.3	0:07.84	java
23858	tg93	20	0	1341m	144m	9588	S	109	1.2	0:07.49	java
23859	tg93	20	0	1351m	137m	9576	S	101	1.1	0:06.47	java
16183	ats	20	0	161m	7912	5496	R	100	0.1	7:23.64	cellmodel
16182	ats	20	0	161m	7700	5300	R	100	0.1	7:31.64	cellmodel
16185	ats	20	0	161m	7604	5296	R	100	0.1	7:04.52	cellmodel
16184	ats	20	0	161m	7776	5532	R	99	0.1	7:28.62	cellmodel
2347	sgeadmin	20	0	99732	3108	1848	S	0	0.0	330:27.68	sge_execd
23241	ats	20	0	10996	1384	908	R	0	0.0	0:00.23	top
1	root	20	0	8352	616	584	S	0	0.0	2:24.91	init
2	root	20	0	0	0	0	S	0	0.0	0:00.95	kthreadd
3	root	RT	0	0	0	0	S	0	0.0	0:11.02	migration/0
4	root	20	0	0	0	0	S	0	0.0	0:19.4	ksftioexecd





... and experimenting with new interaction techniques



- Thanks to EPSRC, Nuffield, and our collaborators at York, Kent, Dundee, Edinburgh and St. Andrews
- Any questions?

