Case study for data visualization using NaviCell Data Visualization Web Service

Prostate cancer cell lines

LNCAP vs. DU145

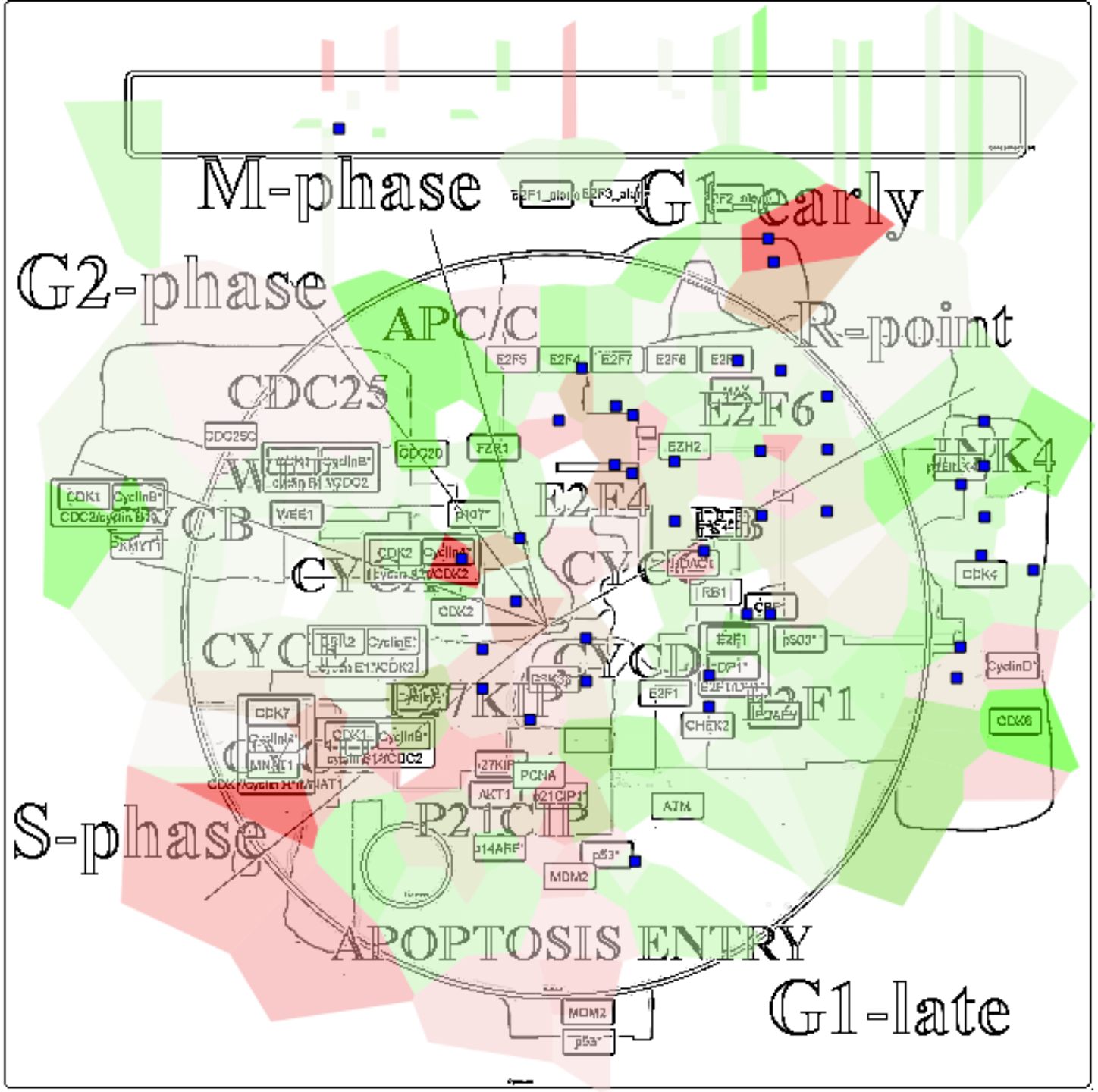
LNCAP vs. DU145 cell lines in Cell Cycle map

Mutated genes from the cell cycle map in both cell lines. There are represented using glyphs (blue dots)

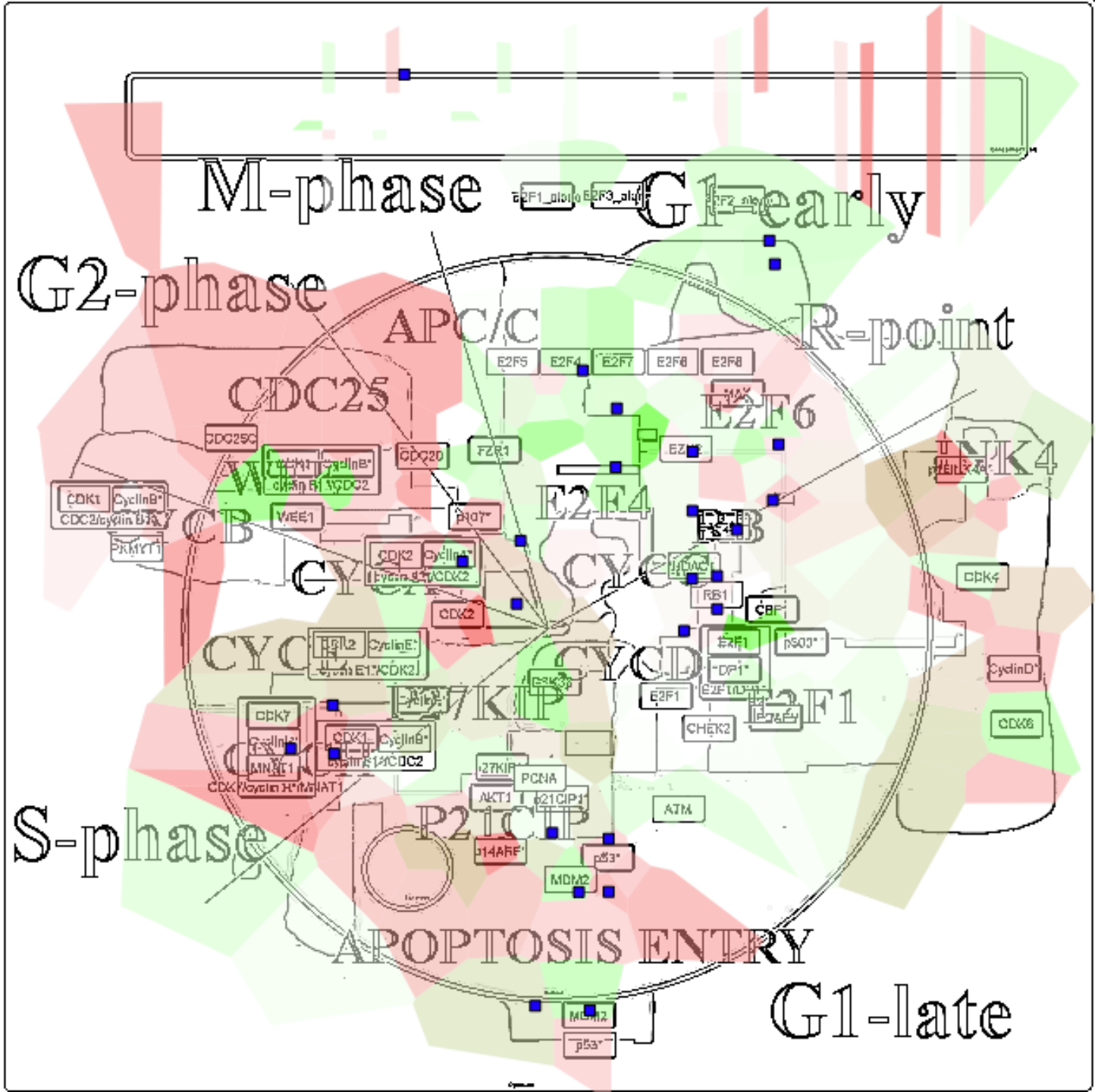
genes	LNCAP_mut	DU145_mut
ATR	K1379N	0
CDK4	P110L	0
CDK7	0	G338_splice
CHEK2	T387N	0
CREBBP	A110V	0
EP300	G1778W	0
HDAC1	E455del	0
MGA	L1902M,E2068*,A1860V	0
RB1	0	K715*
RBL2	K332R	P1119A
TP53	0	V274F

Gene expressions are visualized on the map using map staining function from NaviCell 2

LNCAP


M-phase
G1-early
G2-phase
APC/C
R-point
CDC25
E2F6
INK4
E2F4
CYCB
CYCE
CYCA
CYCD
CIP/KIP
E2F1
S-phase
P21CIP
APOPTOSIS ENTRY
G1-late

DU145


M-phase
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E2F6
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E2F4
S-phase
APOPTOSIS ENTRY
G1-late

Interpretation of the data visualization

For cell cycle map:

If we consider the data as the mean expression of genes of a population of asynchronous cells, most LNCAP cells seem to be expressing genes from the early G1 state (could be considered as the G0 state) and the G1-S checkpoint.

Two interpretations are possible for the LNCAP cells:

- most cells are expressing genes of the G1/S checkpoint. The LNCAP cells could try to overpass the checkpoint with less success than DU145 cells. They remain stuck at the checkpoint.
- the cells are proliferating (going through mitosis) and since G1 and S are the longest phases of the cycle, they might simply represent a higher proportion of asynchronous cells in these phases of the cycle.

For the DU145 cells, genes involved in later stages of the cell cycle seem to be more expressed compared to the LNCAP cells. It can be that if the LNCAP cells were arrested, they have advanced in the cycle by overpassing the G1/S checkpoint and got arrested at the spindle checkpoint (confirmed by the higher expression of the spindle checkpoint module in DNA repair map). They are more prone to proliferate than the LNCAP cells.

We verified the expression of KI-67, a marker of proliferation, and the expression is indeed higher in DU145 than in LNCAP cells (next page). The DU145 is more proliferative than LNCAP cells.

Similarly, mutations (blue dots) seem to be more numerous in later stages in DU145 when compared to mutations in LNCAP.

KI67 marker of proliferation

COMMON	LNCAPCLONEFGC_PROSTATE	DU145_PROSTATE
MKI67	7.52189	9.060399

$\Rightarrow$ Increase in proliferation in DU145 wrt LNCAP

LNCAP vs. DU145 cell lines in DNA repair map

Genes_mutated	LNCAPCLONEFGC_PROSTATE	DU145_PROSTATE	DNA repair map modules
ATR	K1379N	0	G1/S checkpoint; S phase checkpoint; G2/M checkpoint
BRCA2	0	S2284L	HR, FANCONI
CDH1	P700S,P94T	K440_splice	M cell cycle phase
CDK4	P110L	0	G1 cell cycle phase
CDK7	0	G338_splice	G1 cell cycle phase; S cell cycle phase; NER
CHEK2	T387N	0	G1/S checkpoint; S phase checkpoint; G2/M checkpoint
CREBBP	A110V	0	G2/M checkpoint
EP300	G1778W	0	G1/S checkpoint; G2/M checkpoint
ERCC3	A740T,R391W	0	NER
ERCC5	L1023I	0	BER; NER
ERCC6	0	F1437I,Q794H	NER
FANCB	0	G702W	FANCONI; TLS
HSP90AB1	0	D244N	HR; FANCONI; G2/M checkpoint
MEN1	Y318*	0	M cell cycle phase
MLH1	0	A586V,C39_splice	BER; MER; FANCONI; TLS
MSH2	0	L736I	BER; MMR; SSA; FANCONI
MSH3	K381fs	K381fs	MMR; SSA; FANCONI
MSH6	0	S1067I	BER; MMR
MYC	N30S	0	G1/S checkpoint; G1 cell cycle phase
PMS2	0	H189Y	MMR; FANCONI
PRKCB	K489N	P616T	REGULATORS
PRKCH	R271*	0	REGULATORS
PRKCQ	E313*	0	REGULATORS
PRKCZ	0	D275Y	REGULATORS
PRKDC	0	N3605fs	REGULATORS
RAD50	L719fs	N509K	HR; MMEJ; S phase checkpoint; G2/M checkpoint
RAD51B	R18C	0	HR; G2/M checkpoint
RB1	0	K715*	G1 cell cycle phase; S cell cycle phase; G1/S checkpoint
RBBP8	G354fs	S679G	G1/S checkpoint; G2/M checkpoint
TP53	0	V274F	G1/S checkpoint; G2/M checkpoint
TP53BP1	Q106*,R634Q	G1221_splice	G1/S checkpoint; G2/M checkpoint
TP73	Y487H	0	G2/M checkpoint

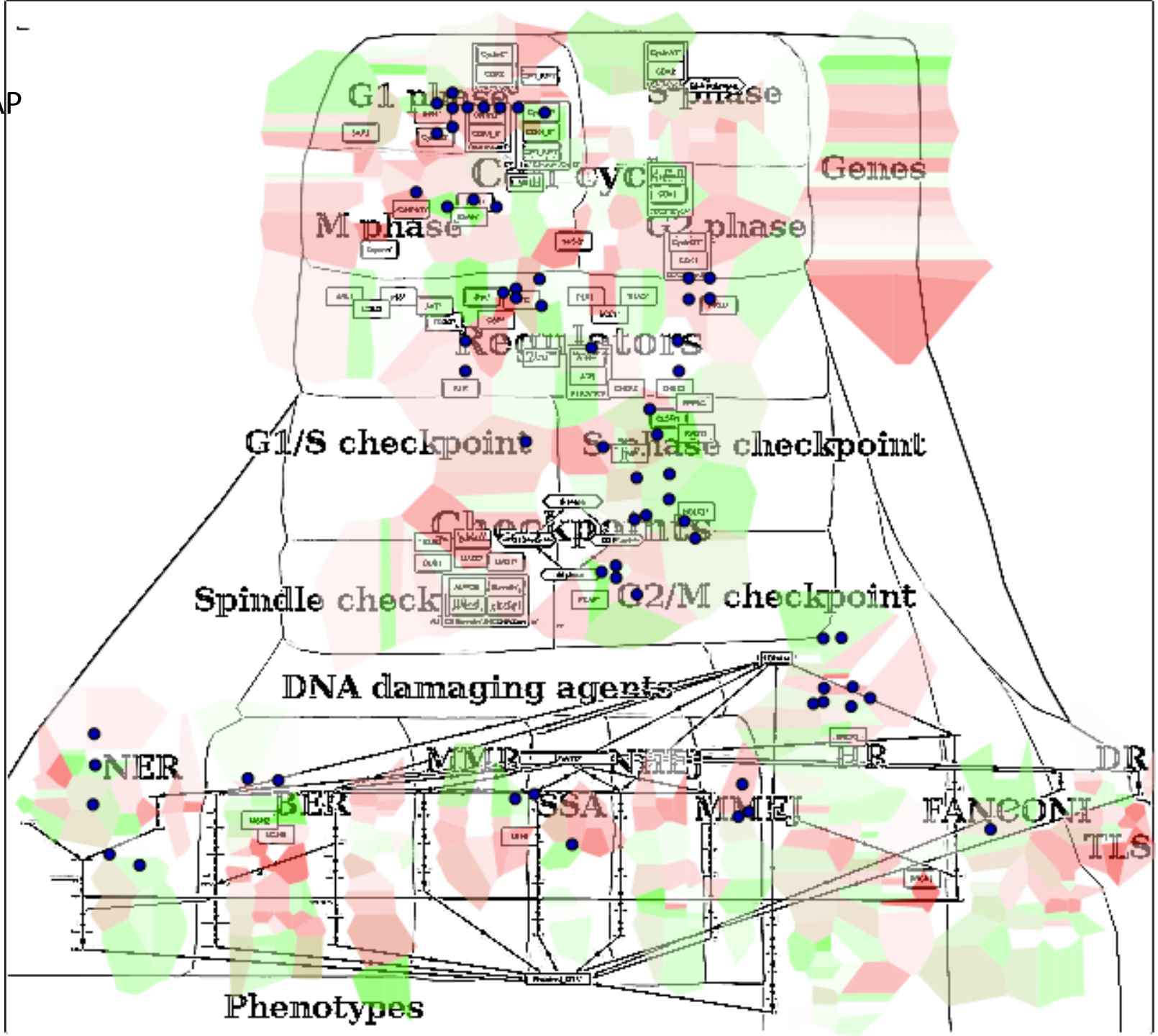
For genes mutated in DU145 cell line, we have highlighted:

- DNA repair pathways (Blue)
- cell cycle or checkpoints (Yellow)

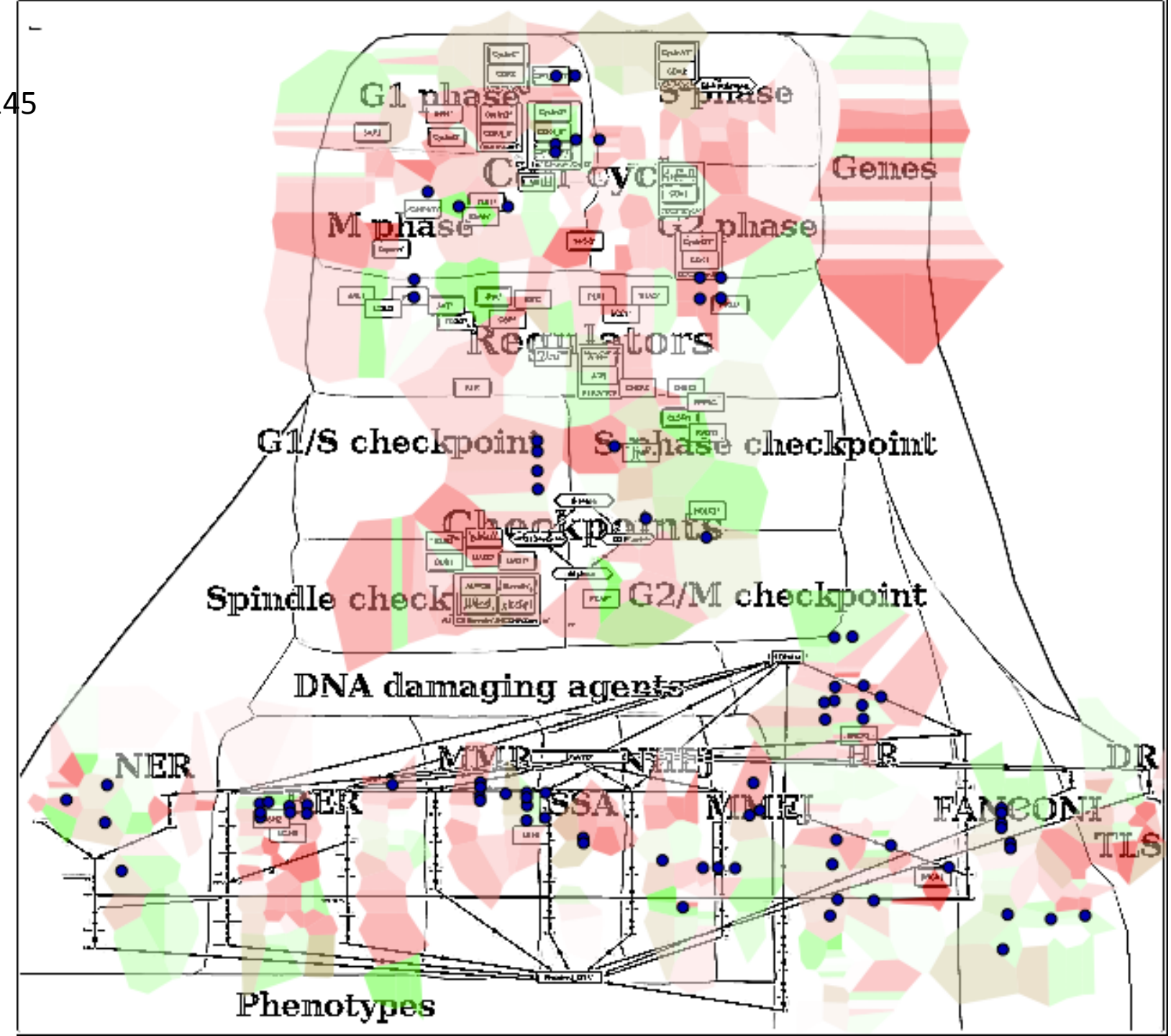
TO KNOW:

1. One mutation may appear several times on the maps: proteins affected by the gene mutations are marked every time they occur on the map. Note that mutations are not known to be activating or inhibiting mutations.
2. Absolute gene expressions are mapped on the map (from 3 to 12)

LNCAP


G1 phase
S phase
Cell cycle
Genes
M phase
G2 phase
Regulators
G1/S checkpoint
S phase checkpoint
Checkpoints
Spindle check
G2/M checkpoint
DNA damaging agents
NER
MMR
NHEJ
HR
DR
BER
SSA
MMEJ
FANCONI
TLS
Phenotypes

DU145


G1 phase
S phase
Cell cyc
Genes
M phase
G2 phase
Regulators
G1/S checkpoint
S phase checkpoint
Checkpoints
Spindle check
G2/M checkpoint
DNA damaging agents
NER
MMR
NHEJ
HR
DR
BER
SSA
MMEJ
FANCONI
TLS
Phenotypes

Interpretation of the data visualization

For DNA repair map:

The mutations in the DU145 cell line are more frequently affecting the regulators of various DNA repair pathways and G1/S, S and G2/M checkpoints, compared to the LNCAP cell line.

The alterations of both the DNA repair pathways and the DNA damage-controlling checkpoints most probably lead to accumulation of DNA rearrangements, and the cells might divide and proliferate even with accumulated DNA damage.

In particular, the mutations in DU145 cell line are affecting multifunctional key regulators of the DNA repair pathways that may alter the activity of several pathways simultaneously. For example, if members of the MSH family are altered (e.g. MSH 2,3,6), single strand DNA damage repair pathways, such as BER, MMR, are affected. In addition, double strand DNA damage repair pathways as SSA, FANCONI seem to be altered as well.

Mutations in the key regulators of HR pathway as BRCA2 and RAD50 responsible for the initiation of the DNA repair pathway, indicate disability of the major double strand DNA damage repair pathway in the DU145 cell line.

References

- Cancer Cell Line Encyclopedia from the Broad Institute and Novartis, containing 883 samples; raw data at the CCLE. Barretina et al. Nature 2012.
- Data extracted from www.cBioPortal.org
  => list of genes composing the two maps: DNA repair and CellCycle from ACSN
- ACSN: http://acsn.curie.fr