# Machine learned-based visualization of the diversity of grapevine genomes worldwide and in Armenia using SOMmelier

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**Abstract.** In the proposed study three major issues have been addressed: Firstly, the diversity of grapevine accessions worldwide and particularly in Armenia, a small country located in the largely volcanic Armenian Highlands, is incredibly rich in cultivated and especially wild grapes; secondly, the information hidden in their (whole) genomes, e.g., about the domestication history of grapevine over the last 11,000 years and phenotypic traits such as cultivar utilization and a putative resistance against powdery mildew, and, thirdly machine learning methods to extract and to visualize this information in an easy to percept way. We shortly describe the Self Origanizing Maps (SOM) portrayal method called "SOMmelier" (as the vine-genome "waiter") and illustrate its power by applying it to whole genome data of hundreds of grapevine accessions. We also give a short outlook on possible future directions of machine learning in grapevine transcriptomics and ampelogaphy.

## 1 Introduction

The grapevine is one of the earliest domesticated fruit crops and has been widely cultivated and prized for its fruit and wine. According to the recent study [1] the roots of domestication were found deep in the Pleistocene, ending almost 11.5 thousand years ago (ya) in the region, where Armenian Highland is existed. Armenia is considered an ancient origin of grapevine domestication and wine-making, which is confirmed by remains of wild and cultivated grapes and wine-producing facilities found at archaeological sites of the country. The diverse climatic conditions, unique geography and existence of wild grapes were the main drivers in the formation of extensive diversity of cultivated varieties and the promotion of wine-making [2].

In the recent decade whole genome studies of grapevine genetic resources using high-throughput sequencing technologies have generated novel knowledge about the evolution of vine traits, genetic diversity, phylogenetic relatedness and historical origin, phenotype associations and migration paths of the vines. There has been a rapid growth in the quality and quantity of data for grapevine genomes, but methods to interrogate this data are limited. At the same time, machine learning and artificial intelligence methods are revolutionising data

analysis. Presented research applied machine learned-based visualization and analysis of grapevine genomic data by SOMmelier method to gain a greater understanding of grapevine genomes, their diversity, function and evolution [3].

Self-organizing neural networks mainly referred to as self-organizing maps (SOMs) were introduced by T. Kohonen in the beginning of 1980's, who presented them as "a new, effective software tool for the visualization of high-dimensional data" [4]. The methods has been further developed into a molecular portrayal method complemented by comprehensive downstream analysis options including different visualization options, knowledge mining and feature selection tasks [5]. It has been applied mainly to different omics data in the human disease context (see, e.g., [6,7]) and recently was applied to a collection of SNP vine genome data [3]. Here we shortly introduce the method, illustrate its power by applying it to worldwide grapevine genomes to reconstruct dissemination of viticulture, discuss the impact of wild and cultivated grapevines collected in Armenia and finally present first results of whole genome analyses using SOMmelier of Armenian grapevine gene pool.

## 2 Machine learning of Vine genomes

Modern high throughput technologies such as genome sequencing revolutionized molecular life sciences. A typical genome-wide data consists of up to millions of items (e.g. single nucleotide polymorphisms, SNPs) for each of the hundreds to thousands of samples serving as input for bioinformatics downstream analysis (Fig. 1). Visualization-based analysis and knowledge mining is a well proven but difficult to realize concept for genomic data because of their size and complexity. We make use of self-organizing maps (SOM), a clustering method which was always developed more than forty years ago [4]. Our SOM-"portrayal" approach uses a very high number of (micro-)clusters largely exceeding the number of relevant dimensions of variation of the data [8]. Particularly, for genomic data of vine the input matrix of size ~$10^8$-$10^4$ is reduced to ~$10^3$-$10^4$ micro-clusters, also called meta-SNPs, because each of them clusters similar SNP-profiles across the vine accessions under study together. SOM clustering uses an iterative, "machine-learning" algorithm to achieve a specific, two-dimensions similarity topology of the clusters. Namely, it arranges them in a two-dimensional array under the condition that neighbouring micro-clusters are more similar (in terms of the *Euclidian* distance) than distant ones. The clustered
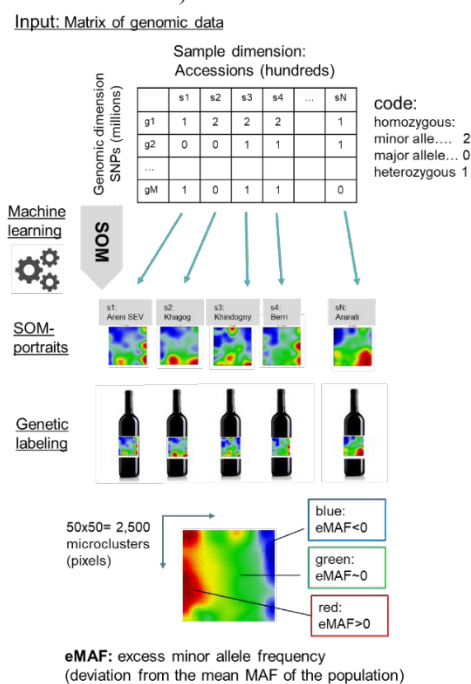


**Figure 1.** SOM portrayal of grapevine genomes (see text).

data are then visualized for each sample by colouring each pixel of the two-dimensional array by the eMAF-value of the meta-SNP, e.g. using a red to blue colour scale. Because of the self-organizing properties of the algorithm the obtained colour patterns exhibit blue and red spot-like regions. They visualize the intrinsic co-variance structure of the data which is specific for each particular genome and can be interpreted as the individual genomic portraits for each of the accessions. Virtually they label each accession by an "fingerprint"-image. The portraits are mutually comparable because the SNPs in

each of the micro-clusters are identical across one SOM. Further, the portraits are interpretable in terms of biological functions, e.g., by applying previous knowledge about functional aspects of the genome and enrichment techniques.

In the scope of proposed study we have analyzed microarray SNP-data of grapevine accession collected around the world and whole genome sequencing data of Armenian wild and cultivated grapevines taken from [9] and [1], respectively.

## 3 Genetic footprints of grapevine cultivation

First, we analysed grapevine genetic SNP- and phenotype data of cultivars collected around the world. The data were taken from [9] and consists of 783 grapevine samples originating from 41 countries in nine geographic regions ranging from Middle Asia to Iberia in the "Old World" and including also New World accessions (see legend in Fig. 2). We calculated country-wise SOM portraits, which reveal overall a high genetic diversity, where, however, portraits of countries from the same region often resemble each other. One finds similarities between the portraits for neighbouring countries from Georgia, via Russia, Ukraine and Moldova, towards Balkan into the west direction and from Georgia and Armenia via Iran towards Tadjikistan, Uzbekistan and Afghanistan in the Middle Asia region. Moreover, the textures alter in a systematic way between the regions, e.g., from the east (EMCA, MFEA) to the west (BALK, WCEU, ITAP and IBER), as visualized by the 'metro-net' lines linking similar country portraits (Fig. 2). Another route is directed from the Caucasus via Lebanon, Israel towards North Africa (MAGH) and Iberian Peninsula (IBER). The South Caucasus is also linked via Anatolia (Turkey), Cyprus and Greece with the Balkan. In the western part of Europe, portraits from Spain show similarities with Northern African countries (MAGH), and only partly with French and German portraits, which, in turn, show similarity links via Switzerland, Austria and the Czech Republic towards Balkan. Mexican cultivars resemble Spanish ones according to their SNP-portraits while cultivars from USA, Australia and Argentina, on average, reflect more similarities with grapevines from MFEA and EMCA.

A recent very large study on the whole genomes of more than 2,000 *V.v.*subsp. *vinifera* and about 1,000 *V.v.*subsp. *sylvestris* disentangles history of grape domestication and dissemination much more in detail [1]. Accordingly, originally grapevine was cultivated separately in an Caucasian and in an Western Asian cultivation centre around 11,000 ya (years ago) and afterwards cultivated grapevine accessions were disseminated across the Old world mainly by Neolithic farmers. Overall dissemination stages refer to six clusters of cultivated grapes (CG1-6), where CG2 refers to the Caucasian origin (blue arrow in Fig. 2), while CG1 and CG3-6 refer to the Western Asian origin (red arrows). The regional similarity relations of the SOM portraits strikingly agree with these CG-clusters.
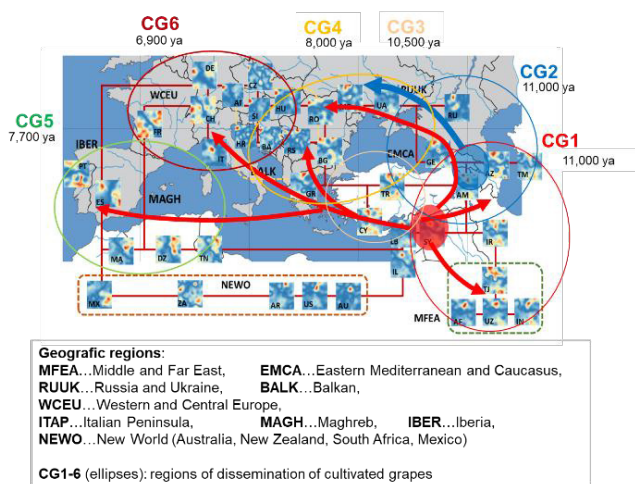
**Figure 2.** Metro map of distribution of cultivated grapes collected from 41 countries around the Mediterranean Sea. Country-wise SOM-portraits are linked by lines according to mutual similarity relations (see [3] for details). The map resembles the dissemination routes of cultivated grapes which originated from two areas of primary cultivation in the Caucasus (blue, CG2) and near East (red, CG1) around 11,000 years ago [1]. CG1 distributed towards the east and the west in the following thousand years as indicated (ya…years ago) and mainly constituted the diversity of grapes observed nowadays. The CG-clusters well agree with the regions included in the ellipses.

The metro-map in (Fig. 2) illustrates country- and region-wise similarities between the grapevine genomes as visualized using their SOM portraits. A complementary perspective in gene-space can be obtained by summarizing the SOM portraits into a genetic overview landscape of grapevine cultivars (Fig. 3). It shows (red) mountain ranges which refer to correlated clusters of SNPs with increased excess minor allele frequencies (eMAF) in the portraits of certain geographic regions as indicated by the flags. Blue coloured areas refer to genomic regions of low eMAF values on the average. Interestingly, the topology of the genetic eMAF-landscape resembles the geographic topology around the Mediterranean and the Black Sea areas including the Caucasus. Namely, the eMAF-'mountains' order cultivars from the Caucasus along a northern route' via Balkan towards Western Europe and along a southern route via Palestine and Maghreb towards the Iberian Peninsula. A central 'blue valley' referring to predominantly low eMAF-values separates both routes. It can be interpreted geographically as the Mediterranean and Black Sea areas, which constitute areas of reduced genetic exchange. Interestingly, the large barrier is found between grapes from the Iberian Peninsula and Western Europe (France, Italy), while the street of Gibraltar appears only as a small sidearm of the central 'genetic' valley, thus indicating a relatively moderate genetic barrier between North Africa and Iberia. Another moderate genetic barrier is found between grapes from the Balkan and Western Europe (Germany, Switzerland and Italy). According to these barriers, cultivars divide into four major groups on the coarsest level of classification, namely Western Europe and Italian grapes, Iberian grapes and vine cultivars from Eastern and

Maghreb regions, which strikingly agree with the CG6, CG5, CG4 (and partly CG2) and CG1 groups, respectively. Detailed inspection of the mountain range of 'eastern' grapes reveals fine internal structure of valleys separating, e.g., Armenian from Georgian grapes and vines from Anatolia and Greece from Balkan ones. Additionally, we visualize grape utilization in terms of phenotype maps which associate table, wine and double usage with different geographic regions (Fig. 3, part below). Grapes for fresh consumption (table vines) predominate in Asia and North African areas, while wine utilization is found mostly in Western Europe. Overall SOM portrayal of grapevine genomes illustrates the specifics of individual grapevine accessions, similarities between them in the historical context of vine cultivation and dissemination as wells as phenotypic traits such as grapevine utilization.
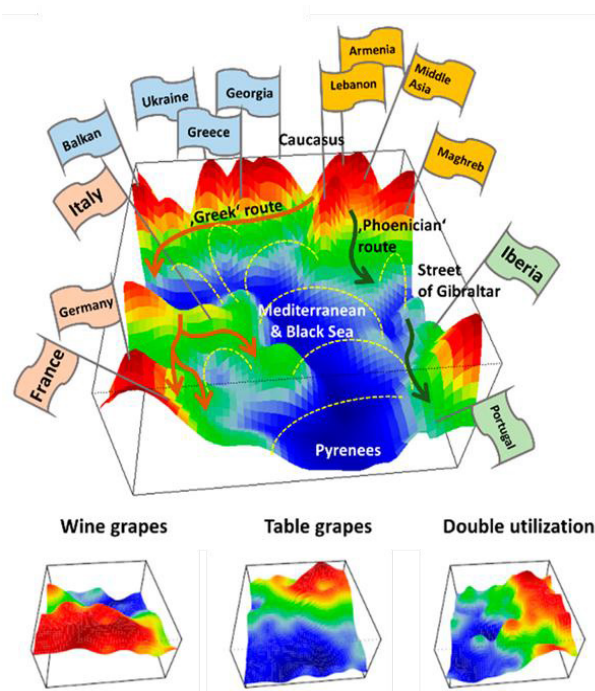


**Figure 3.** The SOM genetic landscape reflects the dissemination paths of cultivated grapes from near east and the Caucasus towards Western Europe and Iberian Peninsula. Grape utilization maps of the grape show preferential wine making in Western Europe, Iberia and Balkan, table grape usage in West and East Asia and double usage in Maghreb and Iberia.

# 4 Diversity of wild and cultivated grapevines in Armenia

## 4.1 Armenian gene pool of *V. sylvestris*

Armenia is an important origin of grapevine domestication, located in the dual domestications centre of grapevine evolution governed by endemic wild grapevines [1]. The country is characterized by a high diversity of cultivated *(Vitis vinifera* L. subsp. *vinifera)* and wild *(Vitis vinifera* L. subsp. *sylvestris*) grapevines. The country has played a leading role in the centuries-lasting history of grapevine cultivation in the Near East.

Varying climatic conditions and the existence of wild grapes lead to the formation and promotion of viticulture and winemaking, as evidenced by nearly 450 autochthonous varieties [2]. Hundreds of unique indigenous cultivars are still preserved in old vineyards and abandoned gardens, though most of them are threatened by extinction. Wild grapes, thriving along riverbanks, climbing the rocks and embracing the trees can be found in Vayots Dzor, Tavush, Lori, Syunik provinces and in Artsakh.

The understanding of the importance of the protection and conservation of genetic resources of the grapevine wild ancestor *Vitis vinifera* L. subsp. *sylvestris* is very high for several reasons. Nowadays, the wild grape population has become relict due to several forms of human disturbance such as habitat destruction and fragmentation, irregular management of the natural environment, pathogen spread, which has increased in the last decades, and a demanding reproductive strategy [10].

Studies on wild grapes reinforced in parallel with the advanced molecular technologies, the ultimate goals of preserving its biodiversity, clarifying its taxonomic status and identifying traits of interest for the breeding program. The study of genetic relationships among the two subspecies of *Vitis vinifera* evidenced genetic relatedness between wild and cultivated grapes in Armenia (Margaryan et al, 2023, accepted for publication in VITIS). The applied hierarchical and non-hierarchical clustering methods differentiated between *sylvestris* and *vinifera*, but also demonstrated existence of gene flow between the wild and cultivated grapevines through overlaps and presence of admixed ancestry values (see also below). High levels of genetic diversity demonstrated by the effective number of alleles and richness of private and new alleles, mirrored the existence of significant diversity both within and between the subspecies suggesting that Armenia is an important centre of grape biodiversity.

## 4.2 Diversity as seen by microsatellite markers

The knowledge of genetic diversity and relatedness among grapevine varieties and wild plants is important to recognize gene pool. One of the major goals more than 10 years for the Group of Plant Genomics at IMB NAS RA was the large-scale research to evaluate the level and relationships of existing genetic diversity of grapes across Armenia, aiming to identify genotypes that could provide genetic insights into the Armenian grapevine germplasm structure. It was confirmed that Armenian grapevine germplasm is a blend of different genotypes, exhibiting a high level of differentiation, resulting in higher-than-expected levels of heterozygosity. This is often observed in woody perennial crops where varieties are selected for their vigor and crop performance, indirectly endorsing high levels of heterozygosity.

Prospections in traditional viticulture regions across Armenia provided insights in the huge grapevine genetic diversity existing in the country. A combination of nuclear microsatellite markers and ampelography proved useful to determine the identity of collected samples recovered from old vineyards and home gardens. Synonyms, homonyms, alternative spellings, and misnomers were clarified. Well-identified and referenced grape genetic resources are a prerequisite for its utilization and the management of germplasm repositories.

The high number of alleles, included also rare and new alleles, high observed and effective heterozygosity values, and presence of female APT3-allele 366, which is absent in western European cultivars, illustrate the huge diversity of Armenian germplasm. Presumably, these findings are related to recurrent introgression of *Vitis sylvestris* into the cultivated compartment during domestication events. Instability of grapevine cultivars also was detected, showing three and in some cases also four alleles at one locus.

## 4.3 SOM portrayal of WGS data

In a new, ongoing project at the Armenian Bioinformatics Institute, a group of young researchers started analysis of whole genome sequencing (WGS) data of wild and cultivated grapevines collected across the viticultural regions of Armenia. This data provided an essential contribution to the understanding of the evolutionary history of grapevine [1]. Phylogenetic clustering separates wild from cultivated grapevines except a small mixed cluster of both (Fig. 4). SOM analysis generated individual portrait of the genomes of each Armenian accession studied. Mean portraits of wild and cultivated grapevines show mirror symmetrical patterns of a red and a blue spot indicating antagonistic eMAF patterns which confirms the separation of accessions in the clustering tree (Fig. 4, part below).
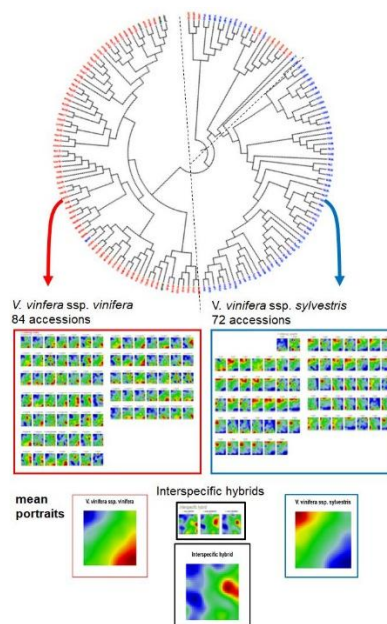


**Figure 4.** Phylogenetic cluster tree of Armenian vine accessions distinguishes *v. sylvestris* and *v. vinifera*. SOM portraits of all accessions are shown in the part below.

## 4.3 Admixture and phenotypic traits

For a closer look we performed admixture analysis assuming *K*=2, 3, 4 and 6 genomic fractions (Fig. 5). For *K*=2 the genomic fractions divide into a (predominantly) *v. vinifera*- (blue colored) and a *v. sylvestris* (red colored) ones in agreement with the phylogenetic tree clustering and SOM analysis (see previous subsection). Hybrid and feral vines show composite genomes with dominant *vinfera*-related fraction. For *K*=3 and 4 one finds a binary, continuously varying composition of *v. vinifera* as well as a binary composition of *v. sylvestris* which however is strongly intermixed with the *v. vinifera* component. Admixture for *K*=6 virtually confirms the *K*=4 analysis.
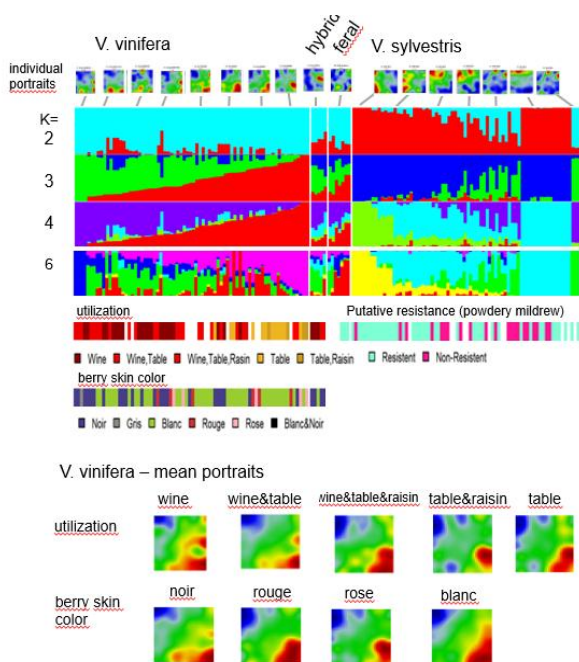


**Figure 5.** Admixture plots for K=2, 3, 4 and 6 components of Armenian wild (*V. sylvestris*) and cultivated (*V. vinifera*) accessions. Selected individual genetic portraits are shown on top of the admixture plot. Part below: Mean portraits over phenotypic traits "utilization" and "berry skin colour".

The individual genetic portraits reveal partly parallel changes of spot patterns and of admixture components which suggest associations between both views but need further analysis. For example, the red eMAF spots rotate in counter clock- and clockwise direction for *V. v. subsp. vinifera* and *V.v. subsp. sylvestris*, respectively, which indicates their systematic variation along the x-admixture coordinate, and, in turn, associates with phenotypic traits such as vine utilization and berry skin colour (see the colour bars in Fig. 5). Phenotype-stratified mean SOM-portraits reveal distinct genetic differences between them. Hence, admixture analysis and SOM portrayal provide complementary information in terms of composite plots along the accession axis and of detailed genetic patterns for of individual accessions, respectively.

## 4.4 Searching for resistance (R-)genes

Out of the 63 *v. sylvestris* accessions studied, 21 (33%) were shown putative resistance against the fungal disease powdery mildew, which enables to search for R-associated chromosomal loci by comparing them on genome-wide scale. GWAS analysis revealed four chromosomal loci significantly associated with resistance against powdery mildew (Fig. 6). SNPs on chromosome 13 are located in an intergenic region corresponding to the previously identified resistance *REN1* locus [11] while the other SNPs suggest possible new R- loci. Mean SOM portraits of Armenian putative resistant and non-resistant *v. sylvestris* accessions show the typical red spot in the left upper corner with slight differences. For higher resolution we generated the difference portrait which, interestingly, shows red R-associated "spots" of increased eMAF in the right upper half of the map and blue spots of decreased eMAF in the left lower part. These patterns suggest a systematic effect of resistance in the vine genomes, particularly, of increased and reduced MAF, respectively. Preliminary results show that selected significant R-SNPs are located in the blue spots of reduced eMAF in the left part of the difference portrait. In summary, potential resistant *v. sylvestris* accessions provide a rich reservoir for the search of R-genes and the underlying molecular mechanisms with potential impact for viticulture. Hereby the combination of GWAS and SOM-portrayal are useful tools for identifying genomic R-loci and mechanisms.
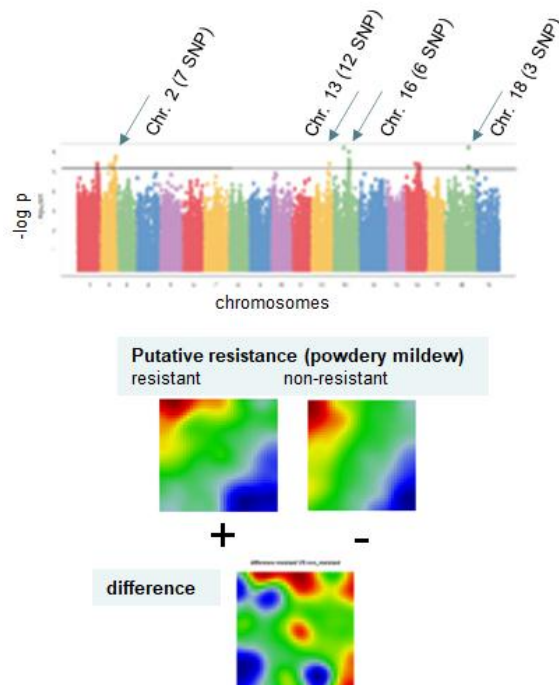


**Figure 6.** Manhattan plot of the results of GWAS on resistant and non-resistant V. sylvestris from Armenia. Mean portraits and their difference are shown in the part below.

# 5 Future aspects of machine learning in vine science

## 5.1 Functional genomics in the era of climate change

Genetics isn't everything! Biological function is governed by a bundle of molecular mechanisms under the effect of environmental condition which includes genomic regulation via an interplay of different omics levels including transcriptomics and epigenomics. Hence, genetic analyses must be complemented by phenotypic and additional omics data for a deeper understanding of grape physiology, e.g. to handle environmental stress in the context of climate change. As an illustrative example we applied SOM portrayal to transcriptomic data (RNAseq) extracted from leaves of grapevines conditioned under different temperature conditions simulating cold-stress [12]. Different stress conditions (freeze stress, chill stress, freeze shock) induce distinct transcriptomic changes relative to the reference "warm" environmental state for five vine accessions (see Fig. 7, part above). Their mean SOM-portraits per condition reveal systematic changes of the transcriptional programs which can be summarized into a merged transcriptional landscape (Fig. 7, part below, red and blue areas indicate over- and under-expression, respectively). The red overexpression modules of co-regulated genes can be assigned to different biological functions specifically activated under the different temperature conditions along a stress-trajectory (white arrow). Hence, SOM-portrayal can be applied to different omics data beyond genetics as a generic clustering, visualization and analysis method for big and complex data collected for studying plant physiology under environmental stress.

## 5.2 Digital ampelography: Learning the shape

"Classical" ampelography generates another type of complex data with impact for classification of grapevine accessions based, e.g., on the metrics of their leaves. It has a long history and can be seen as a sort of "classical" standard based on leave-shapes. We recently developed a SOM-learning method to classify human body shapes [13] which can be viewed as an analogous metric system based on a series of items per human body. Application to ampelographic measures opens one option to handle large-scale leaf data of hundreds of vine accessions using machine learning. Deep learning of leaf shapes represents another, very interesting option for developing and applying digital ampelography techniques to large collections of grapevine varieties [14]. Here, the whole shape of a large number leaves is learned for classification of vine varieties with high accuracy. Digital ampelography is currently in the proof-of-principle stage and needs larger consensus data sets for broad applications. Our contribution will be the systematic gallery of leave shapes of Armenian accessions as well as their machine learning using SOM and deep learning techniques. Furthermore, in a wider sense the individual genetic SOM portraits of vine accessions as presented in chapter 4 can be used for deep learning of genetic patterns for developing a "genetic ampelography". A proof of principle study using deep learning on SOM portraits taken from another application [15] makes its application to vine genomes promising.
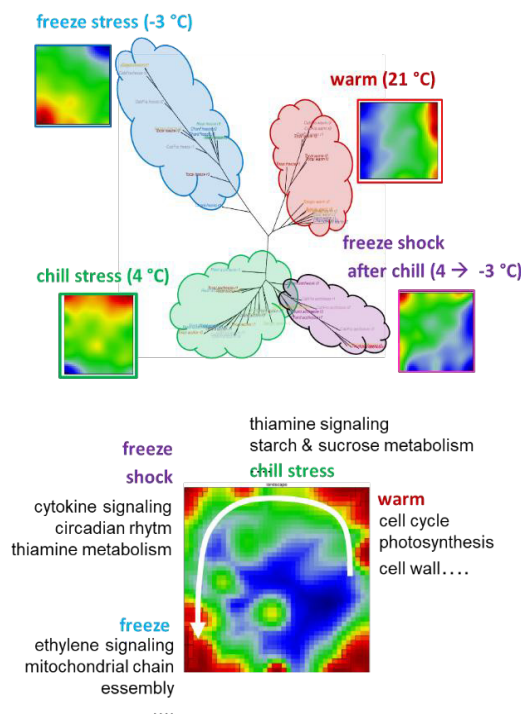


**Figure 7.** SOM portrayal of vine transcriptomics under temperature stress. The phylogenetic tree clusters the transcriptomes extracted from grapevine leaves (five accessions, three replicates) into disjunct clusters, each related to one of the four temperature conditions applied to the plants. Each cluster is characterized by its specific transcriptional state as visualized by its transcriptomics portrait. Part below: the overview landscape summarizes the observed modules of overexpressed genes (red spots), which can be assigned to certain biological functions using previous knowledge and gene set enrichment techniques. The white arrow illustrates a "stress trajectory" pointing from normal, "warm" reference state via cold (chill and freeze shock stress) towards freeze stress. RNAseq data were taken from [12].

# 6 Conclusions

Whole genome data on thousands of grapevine accessions open novel perspectives in viticulture. Machine learning and, particularly, SOMelier molecular portrayal in combination with other bioinformatics methods offers interesting options for their intuitive analysis and understanding in terms of mutual similarities as well as of their functional impact. The detailed study of the richness of Armenian genetic resources is in the focus of our research addressing the history of grapevine cultivation, resistance against fungal diseases and environmental stress in the context of climate change.

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