# Machine learning - could it help in the RIGVIR case?

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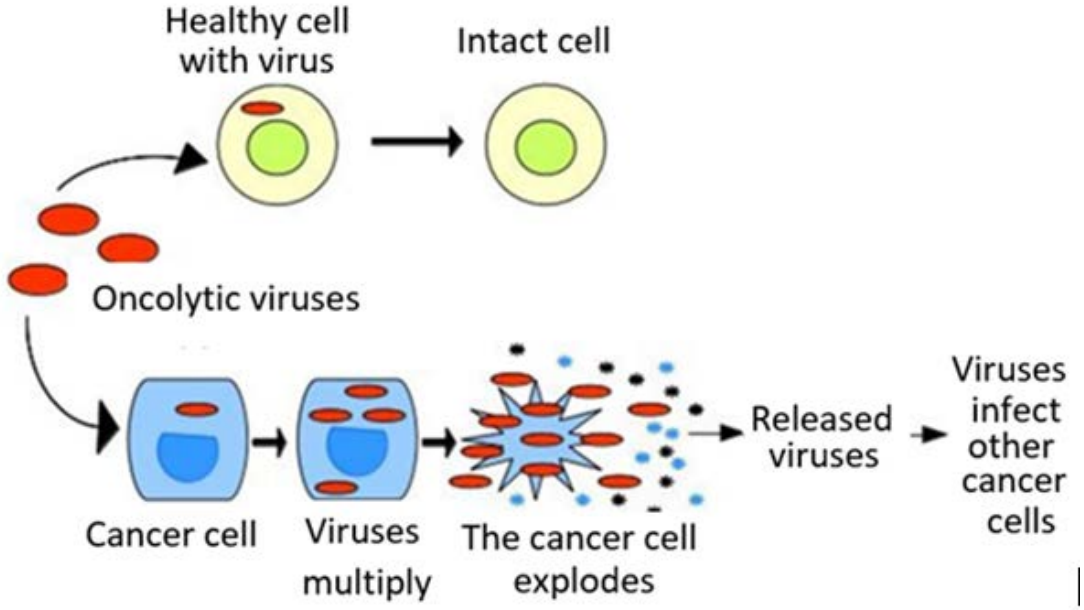
- The RIGVIR story
- Machine learning for skin disease diagnoses
- How to interpret machine learning features
- Discriminant Analysis for automation of diagnoses

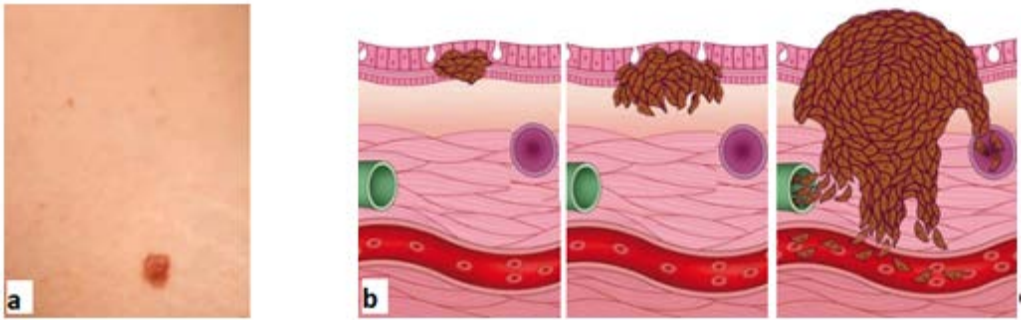
# Introduction

## Schematic representation of oncolytic virotherapy




Viruses can specifically infect cancer cells and then multiply until the cancer cells burst. The newborn viruses are then released to infect (and then burst!) other cancer cells.

# Melanoma is the most dangerous type of skin cancer




a) Melanoma starts from pigment-producing cells,
b) three stages of melanoma, in the third stage it produces metastases.

# Approved oncolytic viruses up to 2021

| Year¤ | Oncolytic·virus¤ | Type·of·tumor¤ |
|---|---|---|
| 2004¤ | ECHO-7·Rigvir·(Latvia)¤ | melanoma¤ |
| 2005¤ | H101·(China)¤ | late-stage·refractory·nasopharyngeal·cancer¤ |
| 2015¤ | T-VEC·(USA)¤ | advanced·melanoma¤ |
| 2021¤ | Teserpaturev·(Japan)¤ | malignant·glioma¤ |

Bifulco, M., Zazzo, E.D., Napolitano, F., et al. “History of how viruses can fight cancer: From the miraculous healings to the approval of oncolytic viruses”. Biochimie. Vol 206, March 2023

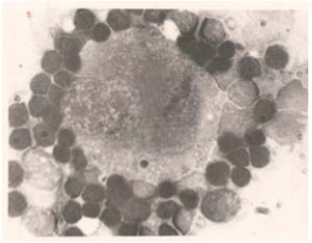
The first oncolytic virus in the world was the genetically unmodified enterovirus RIGVIR, which was approved in Latvia in 2004 for the treatment of skin melanoma.
All other three viruses are genetically modified ones.

RIGVIR is some kind of miracle of nature.

# The RIGVIR story

The research started in Latvia in 1959. The Latvian virologist team isolated 60 different viruses from the gastrointestinal tract of healthy children. One of these viruses called RIGVIR turned out to be the most suitable for oncology. The first RIGVIR clinical trial was approved in 1968.

The pre-registration clinical studies were performed from 1968 to 1991. The first genetically unmodified oncolytic virus RIGVIR was approved in Latvia in 2004 for the treatment of skin melanoma.



Melanoma cell surrounded
by lymphocytes during RIGVIR therapy

**RIGVIR activates immune cells (lymphocytes) - T-cells and B-cells.**

**RIGVIR administration was based on the changes in $CD4^+$, $CD8^+$, and $CD38^+$ lymphocytes.**

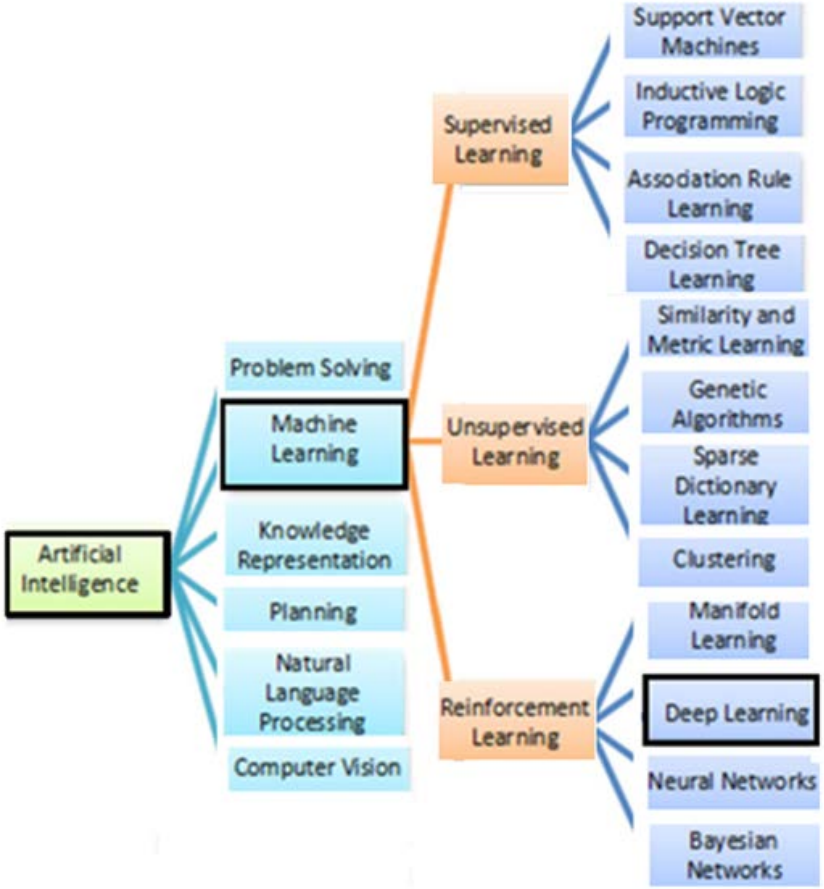
Alberts, P., Tilgase, A., Rasa, A., et al. “The advent of oncolytic virotherapy in oncology: The Rigvir story”. European Journal of Pharmacology. Vol 837, 15 Oct 2018

## KĀ VĒRTĒT IMUNITĀTI (melanomas modelis)

| Melanomas gaitas raksturojums | | Perifēro asiņu imūnšūnu skaita (mm3) un attiecību | | | | | | | Imūnšūnu savstarpējo attiecību simboli | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Ly | > | CD3 | > | CD4 | > | CD8 | CD3/CD4 | CD3/CD8 | CD3/CD38 | CD4/CD8 | CD4/CD38 | CD8/CD38 |
| Kontrole – imūnšūnu skaits/ /attiecības | | 1900 | 1,5 | 1265 | 1,6 | 772 | 1,6 | 490 | 1,6 | 2,6 | 2,5 | 1,6 | 1,5 | 1,0 |
| >, < par 27% | | 2400-1400 | | 1600-925 | | 970-570 | | 620-360 | 2,0-1,2 | 3,3-1,9 | 3,2-1,8 | 2,0-1,2 | 1,9-1,1 | 1,3-0,7 |
| Primārā melanoma | I A stadijā (Cl II) | 1900 | > | 1315 | > | 733 | > | 582 | N | N | N | N | N | N = |
| | I B stadijā (Cl III) | 1900 | > | 1147 | > | 693 | > | 454 | N | N | N | N | N | N = |
| | II A stadijā (Cl IV) | 1700 | > | 1107 | > | 714 | > | 393 | N | N | N | N | N | N = |
| | Reaktīvs limfmezgls | 2000 | > | 1407 | >> | 718 | = | 689 | N | ±↓ | N | ↓= | N | ↑ |
| Primārā melanoma 3 mēnešus pēc radikālas ekscizijas | I A stadija | 2200 | > | 1440 | > | 806 | > | 632 | N | N | N | N | N | N = |
| | I A, I B, II A stadijā | 2100 | > | 1330 | > | 795 | > | 523 | N | N | N | N | N | N = |
| | 3-5 gadu stabilizācija | 1800 | > | 1108 | > | 664 | > | 444 | N | N | N | N | N | N = |
| Limfmezglu raksturojums pēc primārā perēkļa ekscizijas 1 gada laikā | Limfmezgli kliniski normāli | 2125 | > | 1419 | > | 851 | > | 568 | N | N | N | N | N | N = |
| | Limfmezgli reaktīvi | 2500 | > | 1682 | > | 1024 | > | 658 | N | N | N | N | N | N = |
| | Limfmezgli metastāžu periodā | 2700 | > | 1825 | > | 1164 | >> | 661 | N | N | N | N | N | N = |
| | 6-12 mēn. pirms limfadenektomijas | 2151 | > | 1409 | > | 936 | >> | 470 | N | N | ↑= | ↑= | ↑ | N = |
| | I A, I B, II A stadijā limfmezglos | 1600 | > | 1030 | > | 580 | > | 446 | N | N | N | N | N | ↑= |
| | metastāzes reģionālos limfmezglos | 1600 | > | 1046 | > | 626 | > | 417 | N | N | N | N | N | N = |
| Melanomas progresija | metastāzes ādā | 1500 | > | 970 | >> | 490 | = | 480 | ↑= | ±↓ | N | ↓= | N | ↑ |
| | Metastāzes plaušās | 1600 | > | 926 | > | 504 | > | 422 | N | N | N | ±↓ | N | ↑ |
| | Recidīvs | 1600 | > | 1030 | > | 631 | > | 400 | N | N | ↑ | N | ↑ | ↑ |
| | Metastāzes aknās | 1400 | > | 890 | > | 575 | > | 313 | N | N | ±↓ | N | N | ↓ |
| | Totāla progresija | 2450 | > | 1789 | >> | 950 | > | 735 | N | N | ↓ | N | ↓↓ | ↓↓ |

Paskaidrojumi: – protekcijas simptomi – reaktīvo limfmezglu simptomi – progresijas simptomi – indikācijas bioterapijai

Muceniece, Aina, and Venskus, Dita. How to assess immunity (melanoma model). Riga, 2007 (in Latvian).



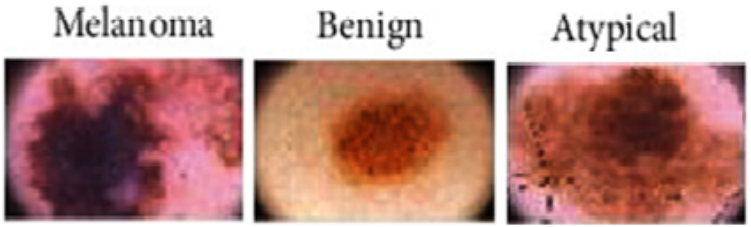

# Artificial intelligence

Machine learning is the heart of artificial intelligence, and its more promising research area is represented by deep learning

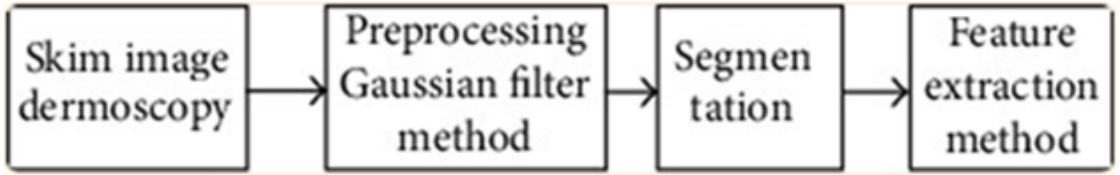
Machine-learning models have demonstrated great success in learning complex.

However, this increased focus has led to considerable confusion about **the notion of interpretability**.

# Machine learning for skin disease diagnoses




Simple images extracted from the database




The skin disease detection using the feature-based method

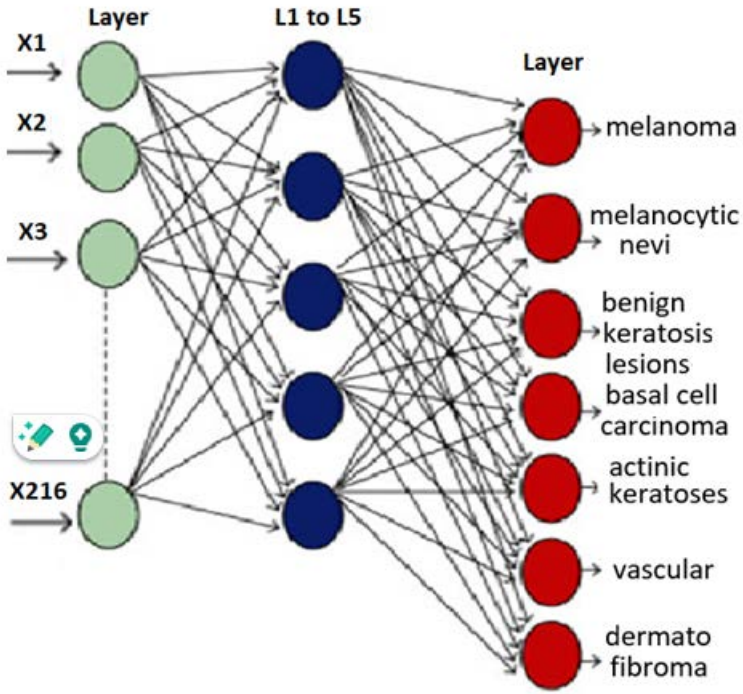
DL model considered 13 statistical features: contrast, correlation, energy, homogeneity, mean, standard deviation, entropy, RMS, variance, smoothness, kurtosis, and skewness.
**216 significant features were selected for training.**

# The architecture of artificial neural network (ANN)

DL model considered 13 different statistical features: 216 significant features were selected for training.

Excellent results have been achieved in the diagnosis of skin diseases. The ANN model achieved the accuracy (98.35%).

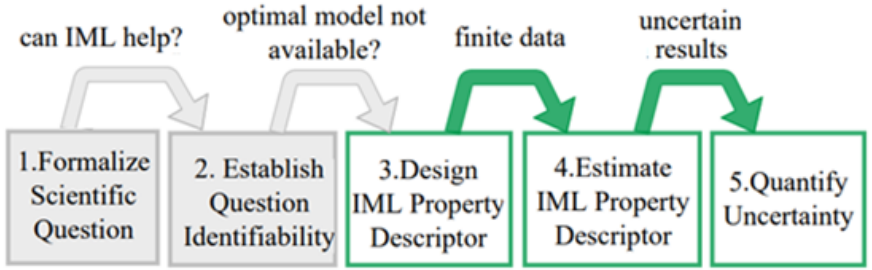
They can certainly speed up the work of doctors (like how an excavator works faster than a man with a shovel). Does it have any value for physician education? Unfortunately, **the doctor is unable to understand 216 computer-generated signs.**




Alsaade, F.W., Aldhyani, T.H.H., Al-Adhaileh, M.H. “Developing a Recognition System for Diagnosing Melanoma Skin Lesions Using Artificial Intelligence Algorithms”. Comput Math Methods Med. 2021 May 15; 2021:9998379.

# On interpretable machine learning (IML)

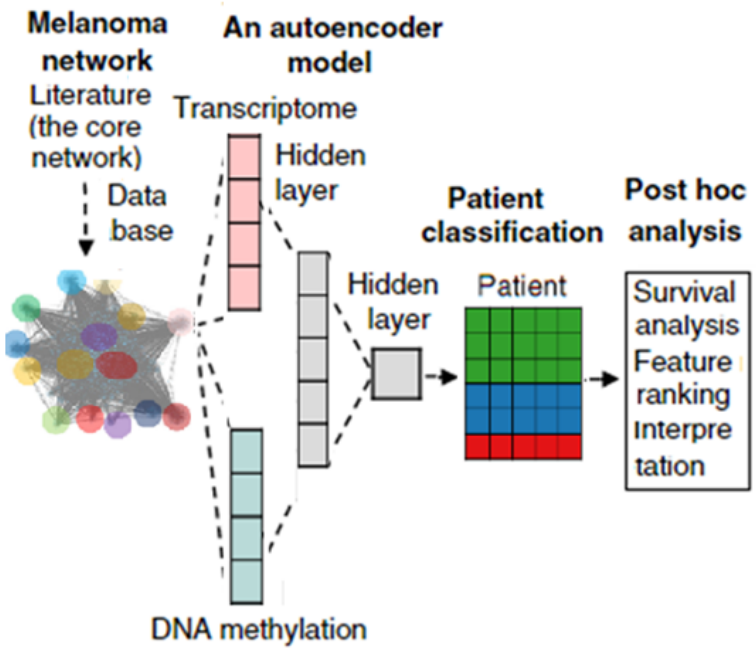
ML models are not elementwise representations
heads of cats (left image), car bodies (center), or bees (right)




An epistemic foundation for scientific inference

Freiesleben, T., König, G., Molnar, Ch., Tejero-Cantero, A. “Scientific Inference with Interpretable Machine Learning: Analyzing Models to Learn About Real-World Phenomena”. June 2022.

# On melanoma genomics and deep learning




Integration of The Cancer Genome Atlas data into a melanoma network

The resulted melanoma network contains 5860 molecules and 14 494 interactions.

| Category | No. of gene symbols | No. of nodes |
|---|---|---|
| Transcriptome (gene expression) | 55 500 | 4983 |
| DNA methylation | 33 487 | 5193 |
| Somatic mutation | 19 303 | 5015 |
| Copy number variation | 19 059 | 4952 |

Overview of the genomics data

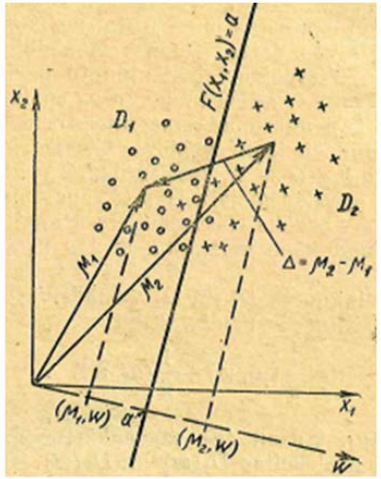
The studied example shows that melanoma genetic research has a very long way to medical practice.

Lai, X., Zhou, J., Wessely, et al. “A disease network-based deep learning approach for characterizing melanoma”. International Journal of Cancer. 150, 6, p. 1029-1044. 15 Mar 2022

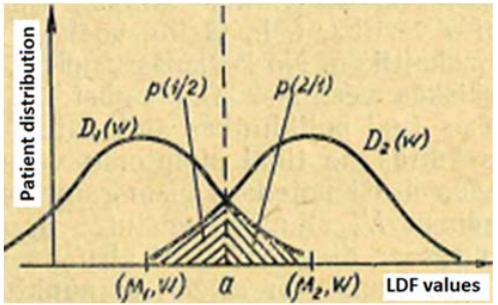
# Discriminant Analysis for automation of diagnoses

Linear discriminant functions (LDF):

$$F = \omega_1 x_1 + \omega_2 x_2 + \cdots + \omega_m x_m$$



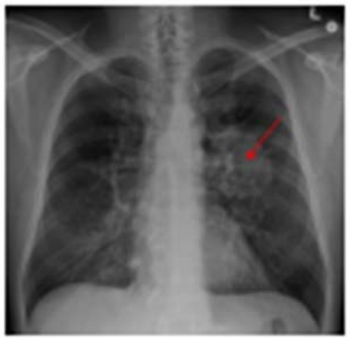

Construction of LDF for two symptoms




Distribution of numerical values of LDF and selection scheme of diagnoses $D_1$ and $D_2$

Sneps-Sneppe, M. A. Mathematics, and Health Care. Moscow, 1982 (in Russian).

# Medical example (1965-1978): Lung Cancer
# Moscow Oncology Research Institute's database



A chest X-ray showing a tumor in the lung (marked by arrow)

How computers can improve diagnostic accuracy

| Diagnostic result | Computer diagnosis | Radiologist diagnosis |
|---|---|---|
| Correct answer | 87.8% | 65% |
| Wrong answer | 4.4% | 10% |
| Refusal to diagnose | 7.8% | 25% |

Statistical analysis, first of all, showed that out of 82 signs (answers to questions) and 240 symptoms of the disease, it is enough to leave 28 signs and 76 symptoms, i.e. 32% of the original data set.

Second, and more importantly, a nurse can fill out a medical chart and receive a diagnosis from a computer without the involvement of a doctor, and this diagnosis turns out to be much more accurate than the decision of a radiologist.

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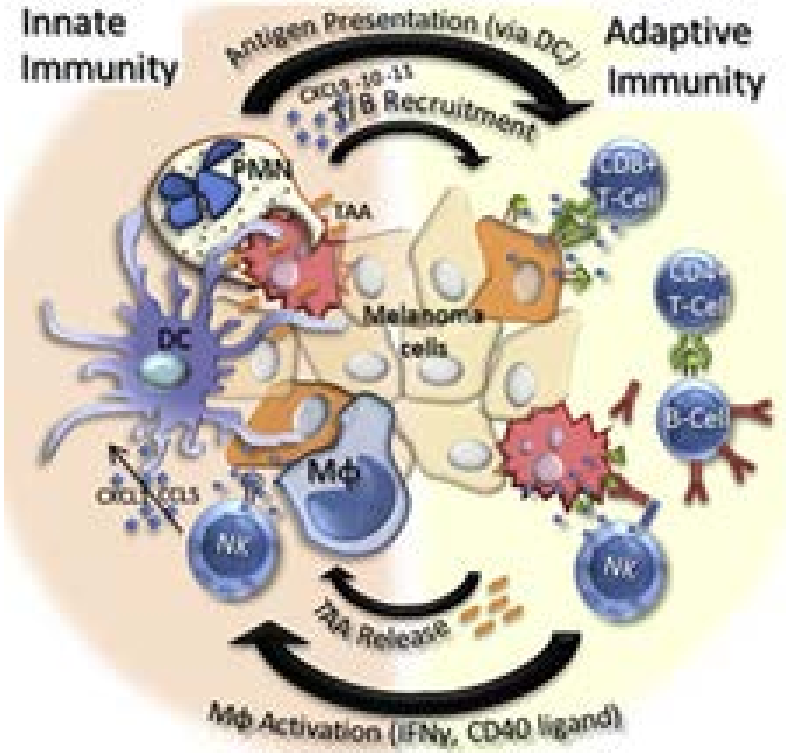
# Melanoma Clearance by Functioning Immune Cells



# Conclusion

The main means of evaluating the effectiveness of melanoma treatment remains the analysis of leukocytes, as in the time of the oncolytic virus RIGVIR discoverer, Aina Muceniece (1924 – 2010).